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Recent Pediatric Literature Confirms Value of CASEC in Breast and Bottle Feeding

Just as DEXTRI-MALTOSE is a *carbohydrate* modifier of choice, so is CASEC (calcium caseinate) an accepted *protein* modifier throughout the year, but especially in summer.

in (1) Diarrhea, (2) Colic, (3) Prematurity, (4) Marasmus, (5) Celiac Disease

"A most satisfactory protein milk for use in **fermentative diarrhea** may be prepared by mixing Casec with cow's milk in correct proportions."

M. A. Bridges: Dietetics for the Clinician, Lea & Febiger, Phila., 1933, p. 535.

"Breast-fed infants with **diarrhoea** should be treated to a short starvation period, then should have 1 to 1½ ounces of the following mixture *before* each breast feeding:

"Casec.....5 packed level tablespoonfuls
"Water..... 10 ounces
"Saccharine..... ¼ grain."

"A large number of the functional diarrhoeas are characterized by acid, excoriating stools and require a relatively high protein diet from the beginning. The non-acid skimmed milk, Casec mixtures for many years have been an effective weapon in the treatment of this group. Three to five ounces of the following mixture may be offered every three or four hours after the starvation period:

"Skimmed milk..... 10 ounces
"Casec.....8 packed level tablespoonfuls
"Water..... 20 ounces
"Saccharine..... 1 grain."

"Carbohydrates must be added to this diet after a day or two, starting with about two level tablespoonfuls of Dextri-Maltose and increasing cautiously (but within a few days to a week, if possible) to six level tablespoonfuls."

H. D. Lynch: The diarrhoeas of early life, J. Indiana M. A. 26:155-159, April 1933.

In feeding the **premature infant,** "Because of the tendency to looseness, it is a wise precaution to add casec (calcium caseinate) to the breast milk in the proportion of 1 tablespoonful of casec to each 3 ounces of breast milk in the total day's feeding."

When treating **marasmus** accompanied by diarrhea, "In severe cases of diarrhoea we may add casec to this feeding, 1-4 tablespoonfuls to the total feeding."

W. A. Hawk: A few of the commoner feeding problems in infancy, Univ. Toronto M. J. 11:218-229, May 1934.

"The infant, in its **immature state,** needs additional protein, calcium and a larger number of calories per pound than the normal infant; thus the addition of 2 per cent calcium caseinate [Casec] fortifies the breast milk to fulfill the infant's needs."

F. M. Martin: Care and feeding of the premature infant, Texas State J. Med. 29:680-684, March 1934.

". . . since protein is of the three food principles the one which the **coeliac** tolerates the best, it would seem that the objection to fresh skimmed milk cannot be maintained, and in point of fact one actually is recommended to reinforce the 'curd' of the milk with casec (calcium caseinate) or curds."

R. E. Steen: Coeliac disease, Brit. J. Child. Dis. 30: 165-180, July-Sept. 1933.

In **celiac disease,** "The initial diet should consist of protein milk, or if this is difficult to obtain, skimmed lactic acid milk to which Casec has been added in the proportion that sugar would be supplied to the normal infant. Skimmed lactic acid milk, without the addition of Casec, is not usually well tolerated."

"Protein milk or skimmed milk, to which, if necessary, Casec has been added, should quickly relieve any **diarrhoea** caused by feeding an excessive amount of fat."

In **premature infants,** "If diarrhoea, rather than vomiting, is present, protein milk powder or Casec may be used instead of the sugar and in the same proportions."

H. P. Wright: Essentials of Infant Feeding and Paediatric Practice, Oxford University Press, London, 1934, pp. 84, 93, 120.

"Calcium caseinate has been suggested above for correcting the **loose stools of breast-fed infants.** This usage can also be applied to the artificially fed infant. The increased protein content of the formula has a constipating tendency, decreases flatulence and thus aids in overcoming **colic.**"

A. F. Abt and B. F. Feingold: The use of powdered milk and milk derivatives in the concentration of infant foods, Arch. Pediat. 47:603-606, Oct. 1930.

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Original Communications

FACTORS INFLUENCING THE EFFECTIVENESS OF PLACENTAL EXTRACT IN THE PREVENTION AND MODIFICATION OF MEASLES

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INTRODUCTION

A REVIEW of the recorded observations regarding placental transmission of immune bodies from mother to offspring, and the demonstrable presence of various antibodies in the umbilical cord blood of infants[1] led to the concept that protein extracts of the placenta might be prepared which would be capable of increasing the protective reaction of infants and children to certain disease processes. Early in our studies it was found that such extracts could be prepared and that by qualitative tests they contained substances, presumably antibodies, which would neutralize diphtheria toxin, blanch scarlet fever rashes, neutralize poliomyelitis virus, and prevent measles in exposed, susceptible patients.[2]

It is the purpose of the present communication to report the progress which has been made in further investigation of these extracts, particularly as regards the factors influencing the practical application of the material on a larger scale to the prevention and modification of measles.

The value of convalescent measles serum or pooled adult immune serum in the prevention and modification of measles has been amply demonstrated. The clinical application of these substances has been hampered by the lack of an adequate supply of convalescent serum and by a marked variation in potency, particularly of adult immune serum. Despite occasional failures, convalescent serum and adult immune

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serum have been extensively used for the control of the disease in ill or debilitated children, especially in institutions. Placental extract held the promise of solving the problem of the supply of the immune substance. Whether the extract could be standardized to give uniformly predictable results has been a major object of investigation.

The presence of several factors which influence the effectiveness of a serum in the control of measles complicates the problem of standardization. It has been thought that (1) potency and (2) dosage of serum in terms of nitrogen concentration of the active fraction in relation to (3) the time of injection were the important items, whether one was dealing with convalescent serum, adult blood, or a preparation like placental extract. However, (4) age and size of the patient and (5) degree of exposure are probably factors, although it is difficult to establish quantitatively their importance. If the potency of the preparation could be standardized, dosage could be adjusted for age and size so that the time of injection of extract would become the factor determining the effectiveness of treatment.

Placental extract has been found in previous studies to be comparable to fresh convalescent serum in that a potent extract given to a nonimmune person in adequate dosage within four days after exposure resulted usually in protection, whereas extract given in the same dosage later in the period of incubation resulted in modification of the disease.[3]

In the attempt to secure uniformly potent extracts, the effect of a variation in antibody content of individual placentas has been overcome by pooling placentas in large lots. The effectiveness of the crude unfiltered globulin extracts had been found to be surprisingly uniform. Crude preparations had been used in 118 susceptible patients exposed to measles without any failures to secure prevention or modification of the disease. However, the crude preparations could not be passed through a Berkefeld filter and, despite repeated tests for sterility, were not deemed to be entirely safe. Consequently an effort was made to determine the fractions of extract which would pass the filter and still be effective against measles.

NOTES ON METHOD OF PREPARATION OF PROTEIN FRACTIONS

Normal-appearing placentas from nonsyphilitic and nontoxic mothers were collected in lots containing from eight to fifty placentas. The umbilical cords were tied to prevent loss of the fetal blood contained in the organs. In earlier preparations the placentas were cut into small pieces with an amputation knife; in later studies the organs were ground very fine in a food chopper. Extraction was carried out with 4 per cent salt solution; in the earlier work 2 per cent had been used. Hypertonic saline was used in order to minimize hemolysis, which occurs rapidly in umbilical cord blood and in the placental extract prepared in isotonic salt solution. About 300 c.c. of the salt solution was added for each placenta. The material was stirred mechanically for half an hour, and at the end of this time the tissue

débris was removed by filtration through cheesecloth after which the blood cells were removed by centrifugation. Extraction of each lot was repeated once or twice so that the total amount of saline used was from 750 to 1,000 c.c. per placenta.

Such extracts contained fetal blood, some maternal blood, and a quantity of placental tissue protein. Because of the association of immune bodies with the globulins of the blood serum of lower animals and presumably of humans, a concentrate of the active material and the removal of inert or noxious matter was sought by separation of the globulin fractions through precipitation with ammonium sulphate. Tests for toxicity and sex hormones indicated that the globulins contained a negligible amount of the hormones and that they were nontoxic for animals even if injected in large doses. Also, by animal tests and clinical trial the antibodies sought were found to be present in the globulin fractions.

Separation of the globulin fractions was carried out by the addition of a saturated solution of ammonium sulphate in such amount as to bring the concentration of the salt up to 50 per cent saturation. The precipitate which formed was collected on filter paper. The filtrates were discarded. The precipitate was dried between folded filter papers, and was then redissolved in salt solution. Reprecipitation served to eliminate in large measure hemoglobin carried down with the globulins.

The final precipitate was placed in cellophane tubes, dialyzed against running water for twenty-four to thirty-six hours, and then against isotonic saline until sulphate-free. The dialyzed extract was adjusted to pH 6.8 (blue green to bromthymol blue). The extracts were somewhat cloudy or muddy appearing suspensions from which a precipitate settled out; this was sometimes centrifugated off and tested separately, designated fraction "FP." Part of the activity against measles was lost in this sediment. The supernatant was put through a Berkefeld V candle after the addition of 1:5,000 merthiolate. Filtration was very difficult, with a further considerable loss on the candles of the material effective against measles.

The fraction obtained by precipitation with one-half saturated ammonium sulphate and containing practically all of the globulins and little albumin has been designated fraction "T."

Subsequently the globulins were separated into two fractions. To prepare the first, or euglobulin fraction, sufficient of the saturated solution of ammonium sulphate was added to the placental extract to bring the final concentration up to 28 per cent saturation. The precipitate formed was collected on filter paper. To the filtrate obtained there was added saturated ammonium sulphate solution to bring the concentration of ammonium sulphate up to 50 per cent saturation. The precipitate obtained by the addition of ammonium sulphate solution to make 28 per cent saturation was very small in amount and difficult to remove from suspension by filtration. Part of this precipitate was insoluble in salt solution. The soluble portion, representing largely euglobulin, was designated fraction "U."

The precipitate obtained with ammonium sulphate between 28 per cent saturation and 50 per cent saturation was quite large in amount and tended to settle out of suspension in a few hours. This precipitate was readily collected on filter paper and appeared to be soluble in physiologic solution of sodium chloride or in Ringer's solution. It was largely pseudoglobulin and was designated fraction "M."

A clear solution which filtered very rapidly could be prepared by removing a water-insoluble fraction at about pH 5.5. This was done by diluting the above final product to eight times its volume with distilled water and adjusting the pH with weak HCl. The isoelectric precipitate so obtained was redissolved and reprecipitated at least once to make the separation more accurate. The filtrates were reprecipitated with ammonium sulphate at one-half saturation, and the precipitate again dialyzed as before. Activity in the prevention of measles was impaired by removal of the isoelectric precipitate.

The isoelectric precipitate removed before separation of the other globulins was designated fraction "P." The 0 to 50 per cent ammonium sulphate precipitate with isoelectric precipitate P removed was designated fraction "S," and that from 28 to 50 per cent precipitation designated fraction "R."

If the original saline extract diluted with sufficient water to lower the salt concentration to 1 per cent was acidified with HCl to pH 5, a heavy flocculent material formed which settled out readily on standing. This fraction was designated "TG"; it was a tissue protein, obtainable only in minute amounts from the blood serum. It was soluble in hypertonic saline and in weak alkalies.

In summary the various fractions investigated, all presumably globulins, have been two ammonium sulphate precipitates, corresponding roughly to pseudoglobulin (fraction R), and euglobulin (fraction U), an isoelectric precipitate (fraction P), and a fraction insoluble in acidified normal salt solution but soluble in hypertonic saline and in alkaline solutions, fraction TG. Various combinations of these fractions have also been prepared.

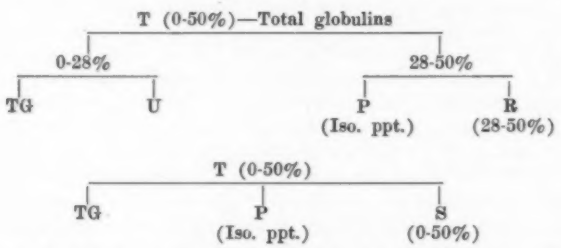

Fig. 1.—Derivation of the various globulin fractions investigated for antibody content. The percentages refer to concentrations of saturated ammonium sulphate used as the precipitating agent.

In Fig. I is shown diagrammatically the derivation of the various fractions.

For further clarity the designations employed for the fractions and the combinations are given in Table I.

TABLE I

PLACENTAL GLOBULINS

Total globulin

T = ppt. in 0-50% $(NH_4)_2SO_4$

Euglobulins

TG = ppt. in acidified 1% NaCl—derived largely from tissue
P = ppt. in acidified 0.1-0.15% NaCl—partly from serum and partly from tissue
U = ppt. in 0-28% $(NH_4)_2SO_4$

Pseudoglobulins

M = ppt. in 28-50% $(NH_4)_2SO_4$
R = M with P removed
S = T with P and TG removed

It is to be emphasized that not all the fractions have been obtained in pure form; a differential precipitation is inadequate for complete separation because the demarcation between the types is not a sharp line, but is rather a zone. Thus in the preparation of any fraction some overlapping of the protein above and below is likely to occur. In the search for the substance active against measles, efforts were made to determine any association of the various immune bodies with distinct fractions.

DISTRIBUTION OF ANTIBODIES IN VARIOUS FRACTIONS

Although complete separation of the fractions has not been possible, the investigation of the association of antibodies with the individual fractions has yielded interesting results. Tests for the diphtheria toxin neutralizing capacity could be made readily on animals, and it was hoped that the diphtheria antitoxin content would parallel other antibodies and that the determination of this substance in various lots of extract might give evidence as to the degree of concentration obtained in the process of preparation, as well as of the potency of other antibodies, notably those like measles which could not be tested for in the experimental animal. The substance neutralizing diphtheria toxin was found to be largely in the pseudoglobulin fractions, with small amounts only in the euglobulins. In an especially purified euglobulin made by repeated precipitations of a water-insoluble fraction derived from a 28 per cent ammonium sulphate precipitate, no diphtheria antitoxin could be demonstrated. Similar results were observed in the search for the substance active in blanching scarlet fever rashes. Mild local reactions to the intracutaneous injections of the extract interfered considerably with this test. However, in cases in which local reactions to the intradermal injection of placental extract did not occur, the blanching substance was found to be present almost exclusively in the pseudoglobulin fractions. Placental extract did not produce blanching of simple erythemas, heat rashes, or drug rashes. Attempts were made to titrate the neutralizing effect of the extract on Dick toxin by injecting intradermally dilutions of the fraction under investigation mixed with standardized doses of commercial Dick toxin. These tests were also clouded somewhat by the tendency of the injection of the extract alone to cause local redness. More striking results have been obtained in attempts to reverse the Dick reaction of patients. Injections of 5 to 10 c.c. of placental extract subcutaneously or intramuscularly into patients with positive Dick tests were found to be followed by a period of several days during which repeated Dick tests were negative. This observation has been made independently by Ross.[4]

In addition to the substance producing blanching of scarlet fever rashes and reversing the Dick reaction, the crude extract was found

to contain an active antistreptolysin. The investigation of the location of this antibody has not been pursued.

From the above observations it became evident that diphtheria antitoxin and scarlet fever antitoxin were to be found almost exclusively in the pseudoglobulin fractions. However, the anticipated parallelism between these antibodies and those to the virus diseases, poliomyelitis and measles, was not observed. On the contrary the virus antibodies, as exemplified by antimeasles activity, were present in roughly comparable amounts in each of three fractions, the euglobulin, the pseudoglobulin, and the isoelectric precipitates. That part of the tissue protein which was insoluble in physiologic salt solution has not been tested in the prophylaxis of measles because of its lack of solubility and the accompanying difficulty of rendering this fraction sterile.

The distribution of antibodies against poliomyelitis was similiar to the distribution of the antibodies against measles. As a result of fourteen neutralization tests, it may be stated definitely that in routine lots both the euglobulin and pseudoglobulin fractions may be expected to contain the poliomyelitis virus neutralizing substance. The tissue protein fraction which is insoluble in 1 per cent saline is also able to effect neutralization. Preserved lots of the various fractions were used in the later neutralization tests after it had been observed that merthiolate 1:5,000 in normal horse serum failed to neutralize the poliomyelitis virus. This finding, together with the fact that one of the fractions even in the presence of the preservative failed to neutralize the virus, indicated that any effect of the preservative on the virus with resultant neutralization falsely attributed to the serum, might be disregarded.

In the present communication only the data regarding the effectiveness of the various fractions in the prevention and modification of measles will be given in any detail.

EFFECTIVENESS OF THE VARIOUS FRACTIONS IN THE PREVENTION AND MODIFICATION OF MEASLES

In the period extending from the time of the inception of the study until Dec. 5, 1934, 1,258 nonimmune children exposed to measles have been given various fractions of placental extract in an effort to prevent or modify the disease. One thousand and eleven of these patients received extracts made in this laboratory, while 247 received an extract prepared commercially. The results of this study are shown in Table II.

It is to be noted in the figures representing the total number of patients treated that the percentage in which protection and modification were obtained was much the same with the commercial preparation as

with our own material. This is of particular interest because the commercial product represented a single type of preparation similar to our S fraction.

TABLE II

PLACENTAL EXTRACT FOR PREVENTION OR MODIFICATION OF MEASLES
TOTAL CASES TO DEC. 5, 1934

SOLUTION (OR FRACTION)	CASES	PROTECTION		MODIFICATION		FAILURE	
		NO.	%	NO.	%	NO.	%
T (0-50)	182	159	87.4	19	10.4	4	2.20
M (28-50)	412	294	71.2	93	22.6	25	6.00
R (28-50)S	99	82	82.8	12	12.2	5	5.00
S (0-50)	181	125	69.2	51	28.0	5	2.76
P Iso. ppt.	100	59	59.0	31	31.0	10	10.00
FP Iso. ppt. removed at end	37	22	59.3	14	38.0	1	2.70
Total	1011	741	73.2	220	21.8	50	5.00
Commercial extract	247	181	73.3	58	23.4	8	3.20
Total cases	1258						

As noted above, the crude unfiltered preparation containing all the globulins (fraction T not filtered) had shown no failures in over one hundred cases. Passage of this material through a Berkefeld filter resulted in a considerable loss of the activity. It is to be noted further that no fraction was obtained which equalled the effectiveness of the crude material or the filtered T preparation, although it would appear that the R fraction (pseudoglobulin) was most nearly comparable in activity and that the P fraction (isoelectric precipitate) was the weakest. However, the differences in the activity of the proteins are more apparent than real because in this table variation in dosage on the basis of total nitrogen content is not considered, nor are the degree of exposure and time of injection given weight.

In order to clarify the factor of degree of exposure and to eliminate the possible inclusion in the total figures of children only questionably exposed to the disease, the total number of cases was subdivided into three groups:

1. Intimate exposure—children exposed at home, to a brother or sister, or to a roommate in a boarding school—all types of exposure in which upward of 90 per cent of nonimmune children could be expected to acquire the disease.

2. Institutional exposure—such as in the hospital where only about one-third of the nonimmune contacts would acquire the disease on exposure to a single case.

3. School exposure—in which contact is casual and infection cannot be presumed to have occurred.

All cases of modified measles and all complete failures of protection in Group 3 were transferred to Group 1, inasmuch as this development demonstrated that such patients had actually been infected with the disease. This procedure obviously swelled the number of failures

and modifications in Group 1 in proportion to the number of complete protections. However, the procedure served to make the test of the extract more stringent. Group 1 represents then the most severe test of the extract. In Table III are shown the results in Group I (intimate exposures) of the use of various fractions of placental extract in the prevention and modification of measles. The cases in this group are also subdivided on the basis of time of administration of extract, so far as the duration of exposure was accurately known. "Given to protect" meant given within four days after onset of exposure. "Given to modify" meant that extract was given from five to nine days after exposure with the intent not of securing protection but of modifying the course of the disease.

TABLE III

INTIMATE EXPOSURE

SOLUTION (OR FRACTION)	CASES	GIVEN TO PROTECT			GIVEN TO MODIFY		
		P	M	F	P	M	F
T (0-50)	26- 25	21	5	0	13	9	3
M (28-50)	47-149	26	14	7	67	67	15
R (28-50)S	16- 19	13	3	0	12	5	2
S (0-50)	29- 49	22	6	1	12	35	2
P Iso. ppt.	16- 36	5	9	2	9	21	6
FP	9- 13	2	6	1	5	8	0
Commercial preparation	24-102	12	11	1	68	30	4
Total	560	101	54	12	186	175	32
Percentage		60.5	32.3	7.2	47.3	45.5	7.2
Percentage		92.8			92.8		

Here again fractions T and R appear somewhat more satisfactory than other portions. It is obvious that the active principle is present in all fractions tested and that each attempt at refinement has resulted in a weakened product. However, these various fractions differed considerably in milligrams of nitrogen per cubic centimeter. The P fraction was particularly low in nitrogen, not because the isoelectric precipitate itself was small in amount, but because the precipitate was so insoluble and difficult to filter. In preparing P fractions for clinical trial, most of the protein was left on the filter candles. The marked variation in nitrogen content of the filtered extracts necessitated a review of the data and a reappraisal of the effectiveness of the various fractions in terms of protein administered in a single dose as measured by milligrams of total nitrogen. The results of this appraisal are shown in Table IV.

The effectiveness of the fractions is considered in relation to dosage of material in terms of nitrogen and with variations in size and age of the patients. It is to be noted that, since the activity of the fractions in terms of nitrogen content was roughly equal, it would appear that the activity as regards measles is distributed throughout the frac-

tions. Furthermore, it is to be noted that for children under two a dosage of 20 to 30 mg. of nitrogen was adequate, but for older children this amount of material was insufficient.

TABLE IV

NITROGEN DOSAGE AND EFFECTIVENESS

	FRACTION	MG. N 5-20			MG. N 21-30			MG. N 31-—		
		P	M	F	P	M	F	P	M	F
Patients 6 mo. to 2 yr.	T	4		1	4			20	2	
	M	20	5	2	43	7		13		1
	R	3	1	2	22	2		6		
	S	8	31		9	1		3	3	
	P	8	6	3	10	1		8		
	FP	1			2			1	1	
Total		44	43	8	90	11	0	51	6	1
Percentage		46.5	45.3	8.5	89	11	0	88+	10.3	1.7
Patients over 2 yr. of age	T	15	5	2	32	6	2	78	5	0
	M	38	10	9	117	44	8	63	19	4
	R	2	1		5	3	1	22	3	2
	S	17	8		34	10		34	18	2
	P	32	17	7		7		1		
	FP	1			4	1		13	12	1
Total		105	41	18	192	71	11	211	57	9
Percentage		64	25	11	70	26	4	76.1	20.7	3.2

REACTIONS

The incidence of reactions of both mild and severe type, which followed the injections of the various protein fractions, is shown in Table V. It will be seen that 23 per cent of the patients had mild local

TABLE V

REACTIONS

FRACTION	TOTAL NO. PATIENTS	NO REACTION		LOCAL		FEBRILE		LOCAL++		FEBRILE (TEMP. 101° + F.)	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
T	207	142	70.0	36	18.0	40	20.0	5	2.4	9	4.4
M	433	314	72.0	99	23.0	35	8.0	8	1.8	4	0.9
R	144	112	78.0	21	14.0	14	10.0	1	0.7	2	1.4
S	228	164	72.0	60	26.0	19	8.0	8	3.5	2	0.9
P	137	71	51.7	56	41.0	32	23.0	10	7.3	5	3.6
	1,149	803	70.0	272	23.7	140	12.4	32	2.8	22	1.9

reactions and that 12 per cent had slight general reactions as indicated by fever. The incidence of severe local reactions was 2.8 per cent; and of more severe febrile reactions (indicated by an elevation of temperature over 101° F.), 1.9 per cent. In no instance did a local reaction persist longer than four days, and in no instance did suppuration occur.

The percentage of reactions was approximately the same for both boys and girls. Age seemed to affect the incidence of reactions in

that reactions were more frequently encountered among older children and adults than among infants and younger children. It is noteworthy that the P fraction, with about half the protein concentration of the other fractions, gave the highest incidence of reactions. This has been attributed to the larger amount of tissue protein in the P fraction. Such an assumption is borne out by the observations from later studies in which methods of extraction were used which resulted in an increase of the tissue protein in the material. The lots from which this tissue protein was not removed caused more reactions than did the lots in which the proteins injected resembled more nearly the blood proteins.

In pursuing this subject the studies of Wooldridge[5] and Mills[6] regarding the coagulative action on the blood of tissue proteins were reviewed. The protein derived from lung tissue and designated by Mills as "tissue fibrinogen" is chemically and physically very similar to our 1 per cent acidified saline precipitate, so-called fraction TG.

Sakurai[7] in 1929 prepared extracts from the human placenta and found that they had the same powerful coagulative action on blood as did animal tissue extracts. Not only would inclusion of certain of the tissue proteins probably be responsible for part of the reaction to the material, but their presence would obviously render the material unsafe for intravenous administration. Filtration seems to remove the bulk of the substance which acts as a coagulant. However, placental extract has not been used intravenously in humans because of this potential danger, although it has been given to rabbits and monkeys in large doses without serious effects. The influence of placental tissue extract on blood clotting will be reported in a subsequent paper.

Immediate and late allergic serum reactions presumably should not occur with a protein of human origin. Nevertheless, three cases of accelerated serum disease occurred among the total number of patients receiving placental extract. Two of these reactions occurred in children known to be allergic; the third child had no previous allergic history.

Injections of placental extract have been found not to sensitize to subsequent injections of the material. A number of patients have received two or more injections at intervals varying from a few weeks to several months. In no instance were the second or subsequent injections followed by local reactions of more severity than were observed after the first injection, and in no instance were there any manifestations of specific sensitization. These findings are in accord with the observations of Nattan-Larrier and Grimard-Richard that fetal serum has no sensitizing action on adults of the same species.[8]

DURATION OF IMMUNITY

Immunity following the injection of placental extract is passive in type and is of short duration. In Table VI are shown results of reexposure of eighteen children within a few weeks after receiving placental extract.

TABLE VI

DURATION OF IMMUNITY
PERIOD BETWEEN INJECTIONS OF EXTRACT AND SUBSEQUENT EXPOSURE

	2 WK.	3 WK.	4 WK.	5 WK.	6 WK.	7 WK.
Number of patients	1	6	6	2	2	1
	Disease modified		Disease not modified			

Eighteen patients were exposed, received extract, and were reexposed.
The time in weeks indicates the period between injection and subsequent exposure.

In view of the short duration of immunity it is doubtful if injection of the material to protect a patient is justifiable outside of institutions except in the case of debilitated, tuberculous, or other acutely or chronically ill children. Rather, the extract should be used to modify the disease and presumably thereby to render the patient permanently immune. That permanent immunity follows modified measles is generally believed, but the number of patients which have been followed is small, so that among the problems that must be solved is the one of how much modification or how little modification of measles will still permit the development of permanent immunity. It is known that, if no measles develop after the administration of serum, the patient again becomes susceptible within a period of a few weeks, whereas, if the typical disease develops, the patient is usually rendered permanently immune. Somewhere between the state of no symptoms and the typical disease lies a stage of enough illness not to endanger the life of the patient, yet to render the child permanently immune.[9] With large-scale studies of measles modification the answer to this question should be found. Modified measles is not known to be followed by complications which render the unameliorated disease a menace. However, here again adequate data on which to base a positive statement are not available.

SUMMARY

Placental extract can be prepared in large amounts and can be made available for the large scale prevention or modification of measles. Attempts to refine and concentrate the measles antibody have resulted in preparations of less potency than the extracts containing all of the globulins. However, the refined preparations can be passed through Berkefeld filters and may therefore be deemed safer to use.

The results in a series of 1,258 cases demonstrate that the refined extracts, although less active than the crude preparations, are still effec-

tive in the prevention or modification of measles. However, this number of tests is inadequate to permit the determination of the best fraction of the extract to use and the dosage required in children of various ages and at various stages of the incubation period of the disease.

The scarlet fever and diphtheria antibodies in placental extract appear to be almost entirely in the pseudoglobulin fraction, whereas the measles and poliomyelitis antibodies appear to be distributed throughout several protein fractions. The tissue protein insoluble in acidified salt solution contains no diphtheria antitoxin but does contain the antibody neutralizing poliomyelitis virus. It has not been tested for activity against measles.

Reactions following the injection of placental extract, although infrequent, appear to be due in some measure to the inclusion in the finished extract of variable amounts of a specific tissue protein. A method of preparation and administration of extract to eliminate reactions is at present under investigation.

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OBSERVATIONS ON THE THERAPEUTIC VALUE OF SPECIFIC IMMUNE SERUM IN EXPERIMENTAL POLIOMYELITIS

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IT IS well established that the serum from monkeys having recovered from poliomyelitis is capable of neutralizing the virus in vitro (Levaditi and Landsteiner,[1] Leiner and von Weisner,[2] Römer and Joseph,[3] Flexner and Lewis,[4] and others). This property is also exhibited by the serum of human beings following recovery from acute poliomyelitis (Netter and Levaditi,[5] Flexner and Lewis,[4] and others). Not only human poliomyelitis convalescent serum, but also the serum of a considerable percentage (about 75 per cent) of the adult population who have to their knowledge not had poliomyelitis may exhibit this property (Aycock and Kramer;[6] Shaughnessy, Harmon, and Gordan;[7] Schultz and Gebhardt;[8] and others). Besides man and monkeys, individual animals in the poliomyelitis refractory group (e.g., sheep, goats, and horses) may respond to repeated injections of poliomyelitis virus with the production of a virucidal serum of more or less high antibody content (Neustaedter and Banzhaf;[9] Pettit;[10] Weyer, Park, and Banzhaf;[11] Fairbrother;[12] Fairbrother and Morgan;[13] Howitt;[14] and Schultz and Gebhardt[15]).

This paper deals with the therapeutic value of poliomyelitis immune serum in the *experimental disease*.

REVIEW OF THE LITERATURE

Comparatively little work on the therapeutic* value of immune serum in experimental poliomyelitis has thus far been reported. Levaditi and Landsteiner[16] in 1910 were apparently the first to report on the value of serum in the experimental disease. They were unable to alter the course of the disease in monkeys by intraperitoneal injections of monkey convalescent serum administered on the same day and one and five days after inoculation with virus. The same year Flexner and Lewis,[17] however, observed that, if the intracerebral injection of virus is sufficiently small (0.1 c.c. of virus filtrate) and followed within twenty-four hours by convalescent serum intraspinally (2 c.c.), one

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*The term "therapeutic," as used throughout this paper, refers to the administration of serum any time after experimental inoculation of animals with virus. In other words, the term is not used in the more restricted sense, sometimes employed, of treatment applied after the onset of clinical symptoms.

may in some cases prevent the development of symptoms. Similar results were reported later by Flexner and Amoss.[18] Neustaedter and Banzhaf[9] in limited experimental observations noted that intramuscular injection of immune horse serum twenty-four hours after intraspinal injection of virus served to prevent the development of symptoms. However, serum administered forty-eight hours after inoculation with the virus failed to modify the experimental disease. Weyer, Park, and Banzhaf[11] have reported a high percentage of survivors following the use of a concentrated globulin fraction of poliomyelitis immune horse serum administered at varying intervals of time after three daily intranasal instillations of virus. The same year Rhoads,[19] however, using the Park serum in an experiment with three monkeys, obtained inconclusive results. Howitt[20] in an extensive experimental study in which convalescent monkey serum was administered by different routes and in varying amounts also obtained what may be regarded as highly inconclusive results.

EXPERIMENTAL WORK

A. *Procedures*

Macacus rhesus monkeys were employed in the studies here reported. The viruses used were the Aycock and the so-called "MV" strains. Both were originally obtained from Dr. Simon Flexner. In the early part of these studies the virus was inoculated by the intracranial route. This route, however, was never regarded by us as altogether satisfactory in a study of this kind. Therefore, before proceeding with the major part of these studies, we carried out an investigation to determine whether the usual incidence of infection by the intranasal route could in some way be appreciably increased. The results of this preliminary work have already been reported (Schultz and Gebhardt[21]). The procedure described has in our hands yielded infection in 90 to 95 per cent of the animals inoculated. The essential features of the procedure are: (1) the use of a mixed virus suspension of high potency (pooled cords from several animals); (2) thorough irrigation of the nasal passages of the animal with a phosphate buffer solution (pH 5) immediately before each instillation of virus; (3) deep ether anesthesia to facilitate carrying out, not only the intranasal irrigations, but also the instillations of virus; (4) three intranasal irrigations and three virus instillations (at about three-hour intervals) *on the same day;* (5) virus instillations made high into the nasal vault, at least 0.5 c.c. of a 10 per cent pooled virus suspension being introduced into each nasal passage with each instillation. Unless otherwise stated, this procedure was followed in all inoculations indicated as having been made by the "intranasal route."

The serum employed in these studies consisted for the most part of poliomyelitis immune horse serum exhibiting an unusually high neu-

tralizing titer in *in vitro* tests. The history of this serum has been described in another paper.[15] It is important to note that this serum in repeated titration studies has exhibited what seems to be the highest virucidal titer of any poliomyelitis immune serum, either of human or animal origin, hitherto reported, a fact which should be kept in mind in reviewing the observations reported further on. Poliomyelitis monkey convalescent serum was employed in several of the experiments. The quantity of serum used and the route by which it was administered are indicated in describing the individual experiments.

B. *Observations*

Experiment 1.—Six monkeys were injected intracranially with 1.5 c.c. of poliomyelitis convalescent monkey serum 1, 6, 20, 30, 42, and 68 hours, respectively, after *intracranial* inoculation (Apr. 10, 1930) with 0.5 c.c. of a 5 per cent suspension of virus-cord. All the animals developed poliomyelitis in six to ten days following the inoculation of virus. Neither the length of the incubation period nor the severity of the disease bore any relationship to the time interval which elapsed before the serum was administered.

Experiment 2.—Two animals were inoculated intracranially (Apr. 25, 1930) with 0.5 c.c. of a 5 per cent suspension of virus-cord. On the first appearance of symptoms, such as tremors, five days later, spinal fluid was removed by lumbar puncture and 10 c.c. of monkey convalescent serum was injected slowly into the lateral ventricles, the lumbar puncture needle being left in place to carry off excess fluid. Both animals, nevertheless, developed extensive paralysis.

Experiment 3.—Six monkeys were injected intracranially (Mar. 17, 1931) with 1 c.c. each of a 1:1,000 virus-cord suspension (aqueous fraction after ether extraction). Four of these animals (398, 399, 400, 401) were given 20 c.c. each of poliomyelitis immune horse serum (Jan. 22, 1931, bleeding[15]) by the intramuscular route on the appearance of tremors and excitability (five days after inoculation). All of the treated animals developed as extensive paralysis as the controls (396, 397).

Experiment 4.—Two monkeys (796, 797) were inoculated with virus by the intranasal route (Oct. 21, 1932). Six days later, and before the appearance of symptoms one of the monkeys (797) was injected with 10 c.c. of immune horse serum (May 3, 1932, bleeding[15]) by the intracardial route. Both the control and serum-treated animal began to show symptoms of the disease on the eighth day and developed essentially the same degree of paralysis.

Experiment 5.—Four monkeys were inoculated with virus by the intranasal route (Nov. 9, 1932). One monkey (830) received no serum, while three were given 10 c.c. each of immune horse serum (May 3, 1932,

bleeding[15]) by the intracardial route. One monkey (831) received the serum twenty-four hours, one (832) forty-eight hours, and one (833) seventy-two hours after inoculation with virus. The control animal developed the disease on the ninth day; the three treated animals on the seventh, eighth, and ninth days. No difference in the extent of the paralysis of the control and the serum-treated animals was noted.

Experiment 6.—Three monkeys were inoculated with virus by the intranasal route (Dec. 14, 1932). Twenty-four hours later two of the monkeys (878, 879) were injected subcutaneously with 20 c.c. each of immune horse serum (May 3, 1932, bleeding[15]). One of the animals (879) developed extensive poliomyelitis ten days later and lived for twelve days thereafter; the other (878) remained well. The control (869) developed moderately extensive paralysis on the fifteenth day.

Experiment 7.—Six monkeys were inoculated with virus by the intranasal route (Jan. 10, 1933). Two monkeys served as controls (900, 901). Each of the remaining animals (902, 903, 904, 905) were given three injections of 20 c.c. of immune horse serum (May 3, 1932, bleeding[15]) subcutaneously two, four, and six days after the intranasal instillations of virus, each monkey receiving a total of 60 c.c. of serum. All animals in the series developed the disease eight days after inoculation with virus, and no important difference was noted in the extent of the paralysis developed by the serum-treated and the control animals.

Experiment 8.—Convalescent monkey serum (pooled serum from eleven monkeys) was used in this experiment. Six monkeys were inoculated with virus by the intranasal route (Jan. 23, 1933). Two monkeys (914, 915) served as controls while the remainder received immune serum by the subcutaneous route. Two of the latter (910, 911) received single injections of 20 c.c. of serum twenty-four hours after virus instillation. Both of these developed the disease six days later. Two monkeys (912, 913) received three injections of 20 c.c. each twenty-four, forty-eight, and seventy-two hours after inoculation with virus. These developed the disease on the tenth and twelfth days, respectively. Both controls (914, 915) came down on the eighth day. The two (912, 913), which had received three injections of serum, were not only slower in developing the disease, but also suffered less extensive paralysis and died nine days (912) and fourteen days (913), respectively, after the remainder had succumbed (which was about three days after the appearance of symptoms).

Experiment 9.—Three monkeys (988, 989, 990) received pooled monkey convalescent serum (from fourteen monkeys); three monkeys (991, 992, 993) received immune horse serum (July 7, 1933, bleeding[15]); and three monkeys (985, 986, 987) served as controls. The serum-treated animals received 15 c.c. of serum by the intracardial

route twenty-four, forty-eight, and seventy-two hours after intranasal inoculation with virus (July 12, 1933), each monkey receiving a total of 45 c.c. of serum.

All of the serum-treated animals developed poliomyelitis eight days after inoculation with virus and presented extensive paralysis within two days after the onset of clinical symptoms. One of the controls (985) remained well; two (986, 987) developed poliomyelitis on the seventh day.

Experiment 10.—Eight monkeys were given the usual three intranasal instillations of virus on May 13, 1934. Twenty-four hours after the last instillation four of the monkeys were injected intramuscularly with immune horse serum (pooled bleedings July 7, 1933 and Jan. 29, 1934[15]) in doses of 2 c.c. per kilogram of body weight. These injections were repeated approximately 24, 48, 72, 96, 120, and 144 hours after the intranasal instillations of virus. The results of this experiment are given in Table I.

TABLE I

MONKEY	WEIGHT IN KG.	AMOUNT OF SERUM PER DOSE IN C.C.	TOTAL AMOUNT OF SERUM IN C.C.	RESULTS
B– 97	2.8	5.6	33.6	Poliomyelitis on 8th day
B– 98	3.0	6.0	36.0	Poliomyelitis on 9th day
B– 99	3.0	6.0	36.0	Poliomyelitis on 9th day
B–100	3.1	6.2	37.2	Poliomyelitis on 8th day
B–101	--	none	none	Poliomyelitis on 7th day
B–102	--	none	none	Poliomyelitis on 10th day
B–103	--	none	none	Poliomyelitis on 7th day

In view of the fact that the serum employed in this experiment was definitely known from previous tests to possess an exceptionally high virucidal titer and was administered in repeated and in relatively large doses, the first dose having been administered twenty-four hours after inoculation of the animals with virus; it would appear that the results of this experiment should be regarded as highly significant. Not only did the serum-treated animals develop the disease after approximately the same period of incubation as the controls, but little, if any, difference was observed in the extent of the paralysis presented by the two groups—treated and untreated.

SUMMARY

The results of ten sets of experiments designed to test the therapeutic value of immune serum in experimental poliomyelitis are summarized in Table II. It will be noted that the observations are surprisingly uniform, despite the fact that the serum was administered in varying quantities by different routes and at varying intervals of time after inoculation of the animals with virus. While several of the

TABLE II

SUMMARY OF RESULTS OBTAINED IN EXPERIMENTS ON THE THERAPEUTIC VALUE OF POLIOMYELITIS IMMUNE SERUM

EXPERIMENT	SOURCE OF IMMUNE SERUM	ROUTE BY WHICH SERUM WAS ADMINISTERED	TOTAL AMOUNT OF SERUM ADMINISTERED (IN C.C.)	LENGTH OF TIME AFTER INOCULATION WITH VIRUS	ROUTE BY WHICH ANIMALS WERE INOCULATED WITH VIRUS	CONTROL MONKEYS					SERUM-TREATED MONKEYS				
						NUMBER USED IN EXPERIMENT	NUMBER DEVELOPING "POLIO"	AVERAGE INCUBATION PERIOD (DAYS)	NUMBER OF SURVIVORS	SURVIVORS (PER CENT)	NUMBER USED IN EXPERIMENT	NUMBER DEVELOPING "POLIO"	AVERAGE INCUBATION PERIOD (DAYS)	NUMBER OF SURVIVORS	SURVIVORS (PER CENT)
1	Monkey	Intracranially	1.5	1 to 68 hr.	Intracranially						6	6	8	0	0
2	Monkey	Intrathecally	10.0	5 days	Intracranially						2	2	5	0	0
3	Horse	Intramuscularly	20.0	5 days	Intracranially	2	2	8	0	0	4	4	8	0	0
4	Horse	Intracardially	10.0	6 days	Intranasally	1	1	8	0	0	1	1	8	0	0
5	Horse	Intracardially	10.0	24, 48, 72 hr.	Intranasally	1	1	9	0	0	3	3	8	0	0
6	Horse	Subcutaneously	20.0	24 hr.	Intranasally	1	1	15	0	0	2	1	12	1	50
7	Horse	Subcutaneously	60.0	2, 4, 6 days	Intranasally	2	2	8	0	0	4	4	8	0	0
8	Monkey	Subcutaneously	20.0 60.0	24 hr. 24, 48, 72 hr.	Intranasally	2	2	8	0	0	2 2	2 2	6 11	0 0	0 0
9	Monkey Horse	Intracardially	45.0	24, 48, 72 hr.	Intranasally	3	2	7	1	50	3 3	3 3	8 8	0 0	0 0
10	Horse	Intramuscularly	33.6 to 37.2	24, 48, 72, 96, 120 and 144 hr.	Intranasally	4	4	8	0	0	4	4	8.5	0	0
Summary of ten experiments						16	15	9–	1	6+	36	35	8+	1	2.8

earlier experiments (1, 2, 3) cannot be regarded as crucial, later ones, in which the virus was inoculated by the intranasal route, seem to leave little to support the possibility that immune serum does appreciably modify the course of the disease once the virus has become implanted in the nervous tissue. The results of Experiment 8 suggest that the pooled monkey convalescent serum may possibly have exercised some therapeutic effect. It, however, is also quite possible that the difference noted between the treated and control animals rests on some factor other than on the use of serum. It seems particularly noteworthy that the administration of serum as early as twenty-four hours after inoculation of the animals with virus, with one exception only, failed to prevent or modify in any significant degree the course of the disease. An explanation of the inability of immune serum to prevent or modify the propagation of the virus, once it is established in the host, is presented in the following discussion.

DISCUSSION

Recent studies on poliomyelitis indicate that from the very beginning of the infection the virus is intimately associated with neurons and that once it is established in the nervous system it is propagated largely, if not entirely, along axonal routes. The evidence for this is varied. In 1930 Fairbrother and Hurst,[22] for example, reported experiments in which after inoculation of virus into the brain or on the nasal mucosa the infection apparently advanced along nerve paths from the cerebral cortex to the thalamus, from there to the medulla, from whence it spreads with almost explosive suddenness to the spinal cord. They noted, moreover, that nerve cell degeneration not only preceded but was often quite independent of inflammatory reactions. Virus was demonstrable in the spinal fluid on rare occasions only. Jungeblut and Spring[23] later in the same year reported the results of an experiment in which the cord of a monkey was transected at the level of the first lumbar vertebra prior to an intracranial inoculation with virus. Nine days following inoculation with virus, typical lesions of poliomyelitis were found in the cervical and thoracic cord while the lumbar cord, which is ordinarily most markedly involved in the experimental disease, presented a normal appearance. Faber and Gebhardt[24] have recently further established the axonal route of dissemination. On sampling different parts of the central nervous system, they found that for periods of less than four days following intranasal inoculation the virus is demonstrable in the olfactory bulb but not elsewhere. By the fifth and sixth days it had spread, apparently entirely by the olfactory tracts and their communications to the hypothalamus where a secondary focus was seemingly established; from whence it spread to the medulla and to the thalamus

and midbrain. It was first detected in the spinal cord on the seventh day and was present at this time in larger concentrations in the cervical than in the lumbar segments. Certain portions of the central nervous system (e.g., cortex, cerebellum) were never found to contain demonstrable quantities of virus, and some evidence was obtained that it may largely or entirely disappear in areas once involved. In an excellent review of this general subject Faber[25] pointed out that clinical observations on man harmonize well with the experimental observations which indicate that the infection is largely limited to individual groups of neurons in the central nervous system.

Further evidence that the virus from the time of the initial invasion propagates itself in very intimate association with nerve cells is afforded by observations recently and simultaneously reported in 1934 by Schultz and Gebhardt[26] and Brodie and Elvidge.[27] This evidence rests on an easily demonstrable fact that after the olfactory tracts have been cut it is no longer possible to infect monkeys with poliomyelitis virus administered by the intranasal route. This simple experiment seems to prove clearly that from the very beginning of the infection the virus is very intimately associated with nerve cells, the initial portal of entry being possibly the terminal hairs of the olfactory nerve. Added to the evidence already presented is the fact that degenerative changes in neurons precede inflammatory reactions in the nearby tissues; furthermore, that intranuclear inclusions and oxychromatic degeneration of the nucleus may be demonstrated in at least a few of the pyramidal cells early in the disease (Covell,[28] Hurst,[29] Schultz[30]). Finally, the results of ultrafiltration studies, which point to virus bodies of a magnitude less than 50 mu. (Clifton, Schultz, and Gebhardt[31]), harmonize with the evidence which points to an *intracellular* infection of individual groups of neurons rather than to a more generalized *intercellular* infection.

In the light of this knowledge it is easy to understand the results obtained in the therapeutic studies here reported. If it is correct that in poliomyelitis the virus is confined largely to neurons and is freed from the infected cells only when they are caused to disintegrate, then it is apparent enough why a complex proteinaceous agent such as immune serum, which although it may bathe the exterior of the cell does not reach the virus established within it. This may also explain the results of serum therapy in other filtrable virus diseases—diseases in which a state of *intracellular* rather than *intercellular* parasitism exists.

Whether or not an immune serum may interrupt the passage of poliomyelitis virus from one neuron to another at their synapses, as has been suggested by Faber,[25] is a possibility which will command consideration in the presence of any proof that serum is actually of

some therapeutic value. Our results do not indicate that immune serum impedes the progress of the virus at any point along its normal path. It is, of course, possible that in the natural disease in man, in which a smaller quantity of virus may be involved and in which the disease tends to progress more slowly, some blocking action may be exercised by serum at the synapsis of neurons. However, the results of recent clinical studies, in which treated and untreated cases have been carefully compared, do not support the possibility that a significant difference exists between the results of serum treatment in the natural and the experimental disease (Park,[32] Landon[33]).

CONCLUSIONS

Specific immune serum is without demonstrable value in the treatment of experimental poliomyelitis.

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APLASTIC ANEMIA FOLLOWING STOVARSOL (ACETARSONE) THERAPY

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FOR the last eighteen months, stovarsol (acetarsone) has been used exclusively in the treatment of children with syphilis in the clinic of the Cincinnati General Hospital. The results of the therapy have been satisfactory in the group of seventy children who have been treated regularly. Complications of the medication have been few in number and of a very mild nature except in the instance of the patient whose illness is reported here.

CASE REPORT

Family History.—The patient's mother died of pneumonia. Her father has been given antisyphilitic treatment. His Kahn test at present is negative. Two brothers of the patient, aged fourteen and sixteen years, respectively, are living and well. One sister, eleven years old, is now receiving antisyphilitic treatment. One sister died at the age of six months, the cause of death being unknown. There is no history of any blood dyscrasia in the family.

Past History.—The patient is said to have been a full-term, normal infant at birth. She has had measles, mumps, and chickenpox, but no serious illness until the present one. In August, 1932, at the age of six years, she was treated in the Pediatric Clinic of the Cincinnati General Hospital for kerato-iritis. The Wassermann reaction was found to be strongly positive and antisyphilitic treatment was instituted on Nov. 2, 1932. Ten doses of a bismuth preparation were administered intramuscularly at weekly intervals, and this was followed by six intravenous injections of 0.1 gm. of neoarsphenamine at the same intervals. These treatments were completed on Dec. 14, 1932. Stovarsol was begun on Dec. 28, 1932, in doses corresponding to the Maxwell-Glaser[1] method. The dosage was as follows:

¼ tablet once a day for one week
¼ tablet 2 times a day for one week
¼ tablet 3 times a day for one week
¼ tablet 4 times a day for one week
½ tablet 3 times a day for one week
½ tablet 4 times a day for one week
1 tablet 2 times a day for one week

Each tablet contained 0.25 gm. of stovarsol. The total dosage for the seven-week course was fifty-six tablets or 14 gm. of the drug. A rest period of one month was allowed between courses in this instance. No other drugs were given during the period of treatment until the patient entered the hospital.

The child received four courses of this medication, completing the last on Sept. 17, 1933.

During the first seven months of antisyphilitic treatment, the child gained 9 pounds, and the only clinical manifestation of syphilis, the kerato-iritis, disappeared except for a small scar which remained on the right cornea. The Wassermann and

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Kahn tests continued to be strongly positive. A red blood cell count made during the last course of treatment was 3,440,000 cells and the hemoglobin was 64 per cent by the Sahli method. At the child's last visit to the clinic on Sept. 10, 1932, it was noted that her skin was rather pale and sallow in appearance, but she had no complaints. She did not return until her admission to the hospital on Nov. 14, 1933.

Present Illness.—On Nov. 3, 1933, the patient, then seven years of age, bruised her right hand in the door of an automobile. The superficial wound was cleaned and dressed, and 1,500 units of tetanus antitoxin were given. A roentgenogram showed no evidence of fracture of the bones. The wound healed well, but within a few days a large bluish area appeared in the surrounding skin which became very painful and tender. Simultaneously, she became listless and complained of aching of the joints. On the third day following the injury, Nov. 6, she had a severe chill which was followed by an elevation of temperature which ranged between 98° F. and 104° F. during the next eight days. The father also noted that the child was very pale. On the seventh day following the injury, Nov. 10, a "gumboil" appeared on the upper left jaw, in the region of the premolar teeth, which was incised. On the night of Nov. 14 the child appeared desperately ill and vomited a small amount of watery fluid; she was brought to the pediatrics ward of the Cincinnati General Hospital.

Physical Examination.—At the time of admission to the hospital, she was in a semicomatose condition. She grunted with each expiration, was restless, and seemed acutely ill. There appeared to be hyperesthesia of the whole body surface. Many purpuric areas were noticed on the abdomen, the lower extremities, and especially in the region of the injury to the right hand. The superficial veins stood out prominently on the pale icteric cutaneous surface. The mucous membranes of the mouth and conjunctivae were almost colorless. There was an old scar on the right cornea. Some hemorrhagic areas were present about the gum margins, and on the gum surface of the upper left jaw there was a circular area of necrosis, 2 cm. in diameter, which was surrounded by an area of redness and edema. A similar lesion was noted on the left tonsil which appeared almost gangrenous. The cervical lymph nodes were moderately enlarged. The respiratory rate was 22 per minute. The percussion note over the chest was not impaired, but on auscultation a suppression of breath sounds was noted and a few medium, moist râles were heard over the right chest posteriorly, especially in the regions just above and below the spine of the scapula. The heart rate was 92 per minute. The area of cardiac dullness was greatly increased in all directions, the apex beat being diffuse and about 3 cm. to the left of the nipple line. At this point a thrill was palpable. A systolic murmur was audible at the apex, and there was a suggestion of a gallop rhythm. The liver was palpable for a distance of 4 cm. below the costal margin. The superficial and deep reflexes were normal.

Laboratory Findings During First Twenty-Four Hours of Hospitalization.—*Blood:* There were 980,000 red blood cells per cubic millimeter, these being well filled with hemoglobin and practically normal in size and shape. The hemoglobin content was 2.35 gm. per cent, or 17 per cent by the Sahli method; white cell count, 2,000. The differential count was lymphocytes, 77 per cent; monocytes, 10 per cent; polymorphonuclear neutrophiles, 7 per cent; eosinophiles, 1 per cent; transitionals, 3 per cent; undetermined cells, 2 per cent. Platelets were practically absent. The clotting time (capillary tube method) was six and one-half minutes. The bleeding time was greatly prolonged. The blood culture was negative. *Urine Examination:* Acid reaction, acetone three-plus, no sugar, no albumin, no blood by chemical test, microscopic examination negative. *Arsenic Content of the Urine:* 0.02 milligrams per cent of As_2O_3 (an amount which was thought to be of no clinical significance).

An electrocardiogram showed signs of diffuse myocardial disease.

Roentgenologic examination of the long bones, the skull, and pelvis revealed no abnormalities in the intimate structure. On Nov. 16, 1933, a roentgenogram of the chest showed an enlarged heart, but the configuration was not pathognomonic of any specific lesion. Rather extensive peribronchial infiltration was present throughout the lungs, suggesting early bronchopneumonia.

Progress.—(See Treatment.) On Nov. 20, 1933, the sixth day after admission to the hospital, the red cell count was 3,285,000. The differential white cell count was polymorphonuclear neutrophiles, 12 per cent; lymphocytes, 79.5 per cent; monocytes, 8 per cent; plasma cells, 0.5 per cent; reticulocytes, 0.1 per cent. Practically no platelets were seen. The red cells were slightly smaller than normal and were well filled with hemoglobin. There was no alteration in the shape of these cells, no stippling, and no nucleated red cells were seen. The polymorphonuclear neutrophiles were mostly of the band form, and certain toxic changes were observed, such

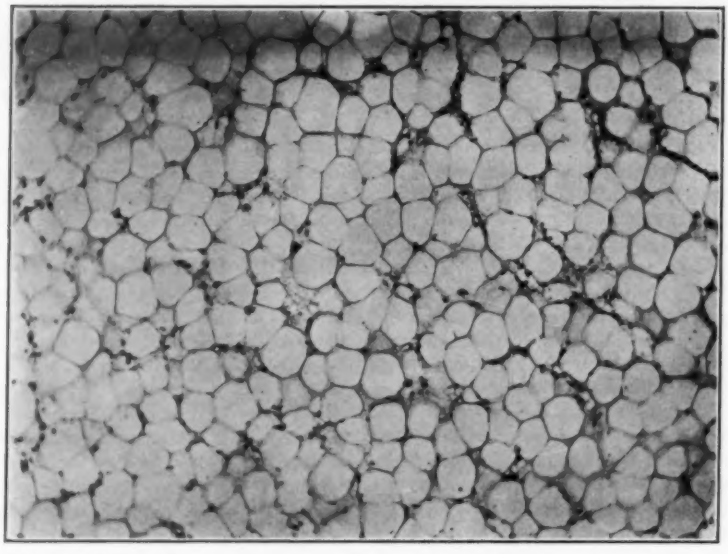

Fig. 1.—Section of bone marrow of the tibia, Nov. 23, 1933. (Low magnification.)

as large, deeply staining granules with some vacuolization. The lymphocytes and monocytes were fairly normal in appearance. The blood picture was that of an aplastic anemia.

On Nov. 23, 1933, a section of bone marrow was obtained from the tibia and stained with hematoxylin and eosin (paraffin section). On microscopic examination the section revealed a great preponderance of fatty tissue with very few blood cells. The blood cells present were mainly of the lymphocytic series with a marked dearth of cells of the myelocytic series. On examination of the entire section only 2 normoblasts were found, and no megakaryocytes were seen. The only cells of the myelocytic series found were a few degenerate polymorphonuclears. The proportion of cells to fat resembled that of adult bone marrow in this region, but the differential count on the cells present would be abnormal even for adult marrow.

Summary: Aplastic bone marrow with striking deficiency in the proportion of cells of the following types: (1) myelocytic, (2) erythrocytic, and (3) megakaryocytic. (Fig. 1.)

The patient's condition remained critical during the first ten days in the hospital. For a few days she was very drowsy and weak, but slowly she became more alert and rational. The restlessness and hyperesthesia disappeared slowly. After each transfusion the color of the skin and mucous membranes improved. The râles in the left chest had practically disappeared by the tenth day, by which time the heart had decreased somewhat in size and the gallop rhythm and thrill had disappeared.

On November 24, the tenth day after admission, a hemorrhage began at the site of the old ulcer on the gum margin; this was checked by the extraction of the upper left premolar and by packing the region. The bleeding time of the patient on this day was one hour. Purpuric spots on the skin were still numerous.

On November 30, the sixteenth day after admission, it was necessary to perform a myringotomy on the left ear drum, and a serosanguineous material drained from this ear for several days. At this time the urine was grossly bloody; this condition lasted for only a few days and was apparently relieved by the transfusions of whole blood.

On Dec. 20, 1933, the red cell count was 3,930,000; the white cell count, 3,700. The differential count was polymorphonuclear neutrophiles, 12 per cent; lymphocytes, 79.5 per cent; monocytes, 8.0 per cent; plasma cells, 0.5 per cent; reticulocytes, 0.1 per cent. Practically no platelets were seen. The red blood cells seemed smaller than normal; there was no poikilocytosis, very little anisocytosis, and the cells appeared to be well filled with hemoglobin. No stippled or nucleated red cells were seen. The polymorphonuclears were mostly of the band form and showed the same toxic changes as on the previous examination. The absence of platelets and the low percentage of polymorphonuclears with marked toxic changes in them demonstrated that the bone marrow was still under the influence of some severe depressant.

On Feb. 5, 1934, the red cell count was 3,600,000; the white cell count, 6,700. The differential count was polymorphonuclear neutrophiles, 27.5 per cent; lymphocytes, 68 per cent; monocytes, 4.5 per cent. The platelets had increased in number since the previous examination but were still below normal. The polymorphonuclears did not show much toxic degeneration. The red blood cells were normal in size, and the appearance of the hemoglobin indicated definite signs of regeneration since polychromatophilia was a prominent feature and normoblasts were seen. The whole picture indicated marked improvement.

On Feb. 7, 1934, she was discharged from the hospital.

Outcome of the Case.—The patient returned to the clinic twice for observation. On each occasion there was a great improvement in her color and general health. The heart had returned to its normal size. The only syphilitic manifestation was the old corneal scar on the left eye. The Wassermann, Kahn and Meinicke reactions of the blood were negative on Apr. 25, 1934, but the Kahn was two-plus on June 20, 1934.

On Feb. 21, 1934, the red cell count was 3,800,000; the hemoglobin, 91 per cent. The differential count was polymorphonuclear neutrophiles, 20 per cent; lymphocytes, 73 per cent; monocytes, 6.5 per cent; plasma cells, 0.5 per cent. The reticulocyte count was 2.5 per cent. The blood picture was about the same as upon previous examination.

On Apr. 25, 1934, the red blood count was 4,320,000; the hemoglobin, 79 per cent; the white cell count, 9,350. The differential count was polymorphonuclear neutrophiles, 55.5 per cent; lymphocytes, 40 per cent; monocytes, 2.5 per cent; plasma cells, 2.0 per cent. Platelets were present in normal numbers. The general condition of the blood had greatly improved since the last examination.

Treatment.—A summary of certain specific therapeutic measures employed during the patient's stay in the hospital is as follows:

Nov. 14, 1933: Blood transfusion, 180 c.c.
Nov. 15, 1933: Sodium thiosulphate, 15 grains. Blood transfusion, 300 c.c., 150 c.c.; glucose and 10 c.c. liver extract intravenously.
Nov. 16, 1933: Sodium thiosulphate, 15 grains; blood transfusion, 250 c.c.
Nov. 19, 1933: Blood transfusion, 300 c.c.; sodium thiosulphate, 11 grains.
Nov. 25, 1933: Blood transfusion, 250 c.c.; liver extract, 23 c.c.

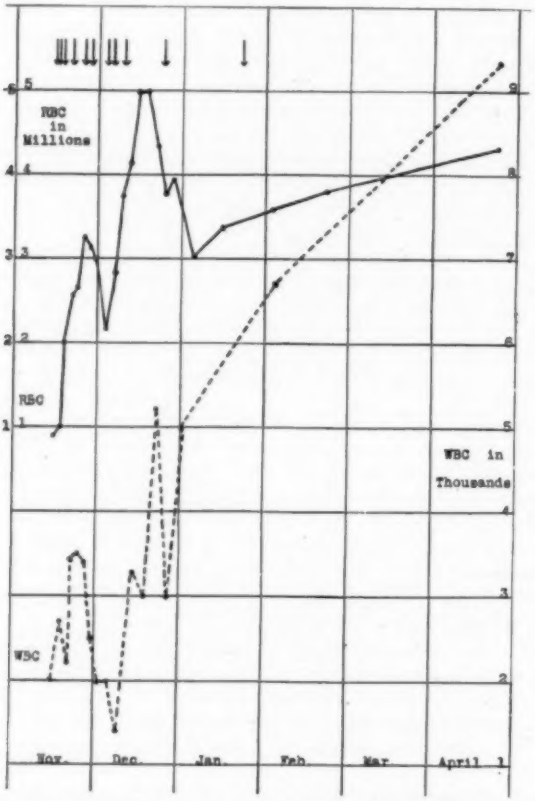

Chart 1.—Illustrating the course of the red and white counts during the illness. The arrows at the top indicate blood transfusions.

Nov. 27, 1933: Blood transfusion, 180 c.c.
Dec. 3, 1933: Blood transfusion, 500 c.c.
Dec. 4, 1933: Pentnucleotide, 10 c.c. intramuscularly.
Dec. 5, 1933: Blood transfusion, 400 c.c.; pentnucleotide, 10 c.c. intramuscularly.
Dec. 7, 1933: Pentnucleotide, 10 c.c. intramuscularly.
Dec. 9, 1933: Blood transfusion, 400 c.c.
Dec. 6, 1933: Addition of vitamin concentrates, liver extract, and iron compounds to diet.

Dec. 14, 1933: Extra calcium added to diet in the form of dicalcium phosphate and calcium gluconate.
Dec. 23, 1933: Blood transfusion, 400 c.c.
Jan. 22, 1934: Blood transfusion, 400 c.c.

A graphic representation of the course of the red and white blood cell counts may be seen in Chart 1.

SUMMARY

The patient was a seven-year-old girl with congenital syphilis, who suddenly developed a severe form of aplastic anemia apparently due to the arsenicals used in the treatment. The antisyphilitic treatment had extended over a period of ten months and had consisted of ten injections of a bismuth preparation, six injections of 0.1 gm. of neoarsphenamine (total of 0.6 gm.) and four courses of stovarsol (total of 56 gm.) Treatment included eleven blood transfusions, and the child gradually improved during the next four months making a complete recovery.

COMMENT

To the best of our knowledge, no previous reports of aplastic anemia following the use of stovarsol have appeared in the medical literature.

Agranulocytosis was observed in a patient treated with stovarsol by W. Haberfeld and M. Rudolph.[2] Agranulocytosis and purpura hemorrhagica occurred in a patient reported by E. Benhamou, P. Temim, and and R. Lofrani.[3]

The rarity of blood dyscrasias following the use of other antisyphilitic arsenicals (arsphenamine, neoarsphenamine, sulpharsphenamine, tryparsamide, etc.) was illustrated by a review of the literature made by F. P. McCarthy and R. Wilson[4] who found reports of only thirty-four cases of aplastic anemia with a mortality rate of 83 per cent; twelve of thrombocytopenia; seven of thrombocytopenia and granulocytopenia; and twelve of agranulocytosis and granulocytopenia.

For assistance in the examination of the blood smears, we are indebted to Dr. Murray Rich, of the medical department, for the determination of the arsenic content of the patient's tissues, to Dr. Robert Kehoe, of the Kettering Laboratory, department of physiology, and for the examinations of the bone marrow sections to Dr. Pearl Zeek, of the department of pathology, College of Medicine of the University of Cincinnati.

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MASKED MASTOIDITIS

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MASKED mastoiditis is commonly defined as a mastoid infection occurring in infants and is characterized by the symptoms of a gastrointestinal intoxication and otitis media. Its existence, however, is still controversial. Hartmann,[1] Marriott,[2] Alden and Lyman,[3] Floyd,[4] Lyman,[5] Odoneal,[6] and Pease[7] observed that mastoiditis may be the primary infection when it occurs in association with infantile gastroenteritis. On the other hand, Maybaum,[8] Johnston and his coworkers,[9] and Wishart[10] were unable to establish any relationship between intestinal intoxication and mastoiditis in infancy.

The evidence of Johnston and his associates against the existence of masked mastoiditis consisted of bacteria of the colon-paratyphoid-dysentery group of bacilli, which they isolated from the stools in acute intestinal intoxication. Wishart,[10] working with the same school, submitted the question to a practical test. Bilateral mastoid antrotomy was performed on thirteen severely toxic infants. He failed to influence the course of the toxemia, and only one infant recovered. He concluded that masked mastoiditis was not the cause of the intestinal disturbance.

The large number of cases of otitis media with gastroenteritis available at the Kings County Hospital offered an opportunity for several clinical and pathologic observations. They are presented as evidence in favor of the clinical entity of masked mastoiditis.

DESCRIPTION OF CASES

One hundred nineteen infants with gastroenteritis and otitis media came under observation from 1930 to 1934. These patients were admitted from the free dispensary whose clientele is composed largely of underweight, undernourished infants. Their ages varied from a few weeks to thirteen months. Approximately one-third were females, and about one-fifth were negro infants.

CLINICAL COURSE AND SYMPTOMS

The clinical course in our patients revealed three stages. In stage 1 the nutritional progress of the infant was suddenly halted by fever. Examination revealed otitis media. Following myringotomy or spontaneous perforation of the eardrum, fever subsided, and the few-ounce loss was frequently regained. The ear drainage persisted. Stage 2 was characterized by occasional vomiting, an increase in the number of

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stools, which became slightly watery, a gradual loss of weight, and a low-grade fever. Stage 3 set in from several days to two or three weeks following the opening of the eardrum. The onset was notably tempestuous. The temperature rose acutely from three to five degrees, and simultaneously the weight fell 8 to 30 ounces. The infant now presented the common picture of acute intestinal intoxication. Diarrhea and vomiting became severe; dehydration was rapid; weight fell in spite of supportive therapy; anorexia was common; the infant was apathetic and rarely cried. Unoperated or late operated cases usually proceeded to athrepsia, cachexia, and death.

Two variations from the customary clinical course were noted. In some instances stage 1 was rapidly followed by stage 3. In another small group a milder course was observed, in whom dietetic measures proved unavailing, whereas mastoid antrotomy resulted in rapid recovery.

It is our opinion that the mastoid infection set in coincident with stage 2; but the failure of the infants' resistance precipitated the profound toxemia of stage 3.

DIAGNOSIS

The diagnosis of masked mastoiditis depended entirely upon the clinical picture described. The classical symptoms and signs of mastoiditis were rarely present. The x-ray examination was not relied upon since many proved mastoid infections produced normal roentgenograms. The swelling of the posterior superior canal described by Lyman[5] frequently occurred too late to be of value.

ANALYSIS OF CASES

A. *Analysis of Surgically Treated Cases.* Fifty patients were submitted to operation. This consisted of bilateral mastoid antrotomy and in a few instances, of unilateral antrotomy. At operation pus, granulations, and sequestrums of bone were found. There were twenty-three recoveries, a mortality of 54 per cent.

These cases were studied to determine the conditions that influence the prognosis. One factor appeared to exert a striking effect upon the mortality. Calculating the percentage of loss of weight, determined from the onset of the ear infection to the day of operation, it was evident that an acute loss of weight of more than 10 per cent frequently foreshadowed a fatal outcome for the patient. Upon this basis, further analysis of the fifty cases submitted to operation disclosed that of twenty-six patients who had lost less than 10 per cent of weight at the time of operation, there were twenty-one recoveries, a 19 per cent mortality; while of twenty-four patients who had lost more than 10 per cent of weight, there were only two recoveries, a 92 per cent mortality.

B. *Analysis of Medically Treated Cases.* Sixty-nine patients presented the syndrome described but were not operated upon. Only ten infants recovered, a mortality of 85.5 per cent. These patients were

treated with transfusions, dietetic changes, hypodermoclysis and phleboclysis. The mortality of this group and that of the group operated upon after a 10 per cent loss of weight appeared significantly alike.

ANALYSIS OF AUTOPSIES

There were twenty-five autopsies in this series—eleven from the surgically treated group, and fourteen from the medically treated group. In the former the operative diagnosis was verified. An acute inflammation of the meninges was present in one patient. In the medically treated group otitis media and mastoiditis were demonstrated in all. In addition, osteomyelitis of the petrous bone was discovered in two patients and a sinus thrombosis, in one.

Many otologists are under the impression that the antrum of an infant normally contains débris and cloudy material. On this basis they are frequently skeptical of the diagnosis of mastoiditis made at the operating or autopsy table. Wishart[10] made a controlled study of the infant antrum at autopsy. He observed that the mastoid antrums of infants at autopsy were as a rule healthy and that the presence of infection or accumulations was antemortem in origin. Our own observations confirm these conclusions.

TREATMENT

The operation consisted of bilateral mastoid antrotomy and drainage performed, in most instances, under local anesthesia. The simplicity of the procedure offered practically no operative risk. Rabbiner[11] reported nine cases of masked mastoiditis. He concluded that unilateral antrotomy in the presence of bilateral otitis media proved inadequate. Our experience coincides with this view, for it is possible that there may be a localized pocketing of pus on the other side.

Supportive measures were used before and after operation. It served to increase and elevate the patient's resistance until the infection subsided.

Many physicians unfortunately believe that operation is indicated only if the patient has the classical signs of mastoiditis or that operation is not necessarily urgent and should be postponed as long as possible. Such temporizing seems to carry a high mortality rate and is contrary to the general surgical principle that an operative procedure offers less risk before the infant has become cachectic and athreptic.

The otologist and pediatrician should realize that this disease represents an emergency comparable to an acute appendicitis. Surgical intervention should be instituted before there is a severe loss of weight. It is only in this way that the mortality can be appreciably diminished.

CONCLUSIONS AND SUMMARY

Undernourished, underweight infants were found especially susceptible to masked mastoiditis.

The disease seemed to follow a distinct clinical course and was manifested by otitis media and gastroenteritis.

The prognosis depended upon early bilateral mastoid antrotomy, as evidenced by our mortality statistics.

The mortality in the medically treated group was 85.5 per cent.

Bilateral mastoid antrotomy carried a mortality of 54 per cent.

Operation performed before there was an acute loss of more than 10 per cent of the body weight carried only a 19 per cent mortality.

Operation performed after there was an acute loss of more than 10 per cent of the body weight carried a 92 per cent mortality.

The response to early operation evidenced by the rapid regression of the intestinal symptoms and prompt response to supportive therapy warranted the diagnosis and defended the treatment.

We are indebted to Dr. George Brockway, attending in pediatrics, for helpful advice and guidance in this study.

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ACUTE LYMPHATIC LEUCEMIA IN CHILDHOOD

A Study of Sixty Cases With Especial Reference to the Cytologic Characteristics of the Blood

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ACUTE lymphatic leucemia, although a relatively uncommon disease, occurs not infrequently in childhood. Warren[1] in 1928 gathered reports of 500 cases from the literature, beginning with the first description of the acute form of lymphatic leucemia by Friedereich[2] in 1857. Sixty cases of acute lymphatic leucemia among children have been observed at the Mayo Clinic between the years 1921 and 1933, and from them an analysis has been made of the clinical and hematologic findings.

In more than half of the sixty cases the patient was in the first four years of life, the youngest being eight and a half months of age and the oldest, thirteen and a half years. Males predominated over females in the ratio of 36:24. This predominance was especially marked during the first four years of life when males outnumbered females two to one. The predominance of the disease among males has generally been recognized by Warren, Ward,[3] and Ordway.[4] The tendency for the condition to affect children in the age group from one to four years has been mentioned by Ramsey,[5] who found in his series of 100 cases among children that twice as many children in this age group were affected as were those in the group between the ages of four and eight years. The incidence of the disease in cases included in this paper is given in Chart 1.

The clinical picture of the disease is so generally known that little need be said about it here. The onset of the condition was often insidious and began with an infection of the upper portion of the respiratory tract in more than half of the cases. Infections of the respiratory tract are not generally recognized as precursors of acute leucemia, and the frequency of their occurrence in the present series is to be emphasized. Warren has drawn attention to this and classifies the prodromal symptoms into three groups: (1) sore throats and enlarged tonsils, (2) ulcerative stomatitis, and (3) "colds that hang on."

Pallor and enlargement of lymph nodes, usually of those of the cervical group, were the most frequent initial symptoms, and they occurred in fifteen and fourteen cases, respectively. The next most common initial symptoms were cachectic in nature and occurred in ten cases; these included weakness in four, listlessness in three, irritability in one, and restlessness at night in two. Less frequent were pains in the extremities and hemorrhages, which occurred in six and three cases, respectively.

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The relation of subjective symptoms appearing first as initial symptoms and then later after the onset of leucemia was as follows: fever and night sweats were initial symptoms in two cases and appeared after the onset of leucemia in twenty-four; weakness was initially present in four cases and later in nineteen; anorexia occurred initially in none but later in eighteen; listlessness occurred initially in three and later in twelve; irritability initially in one and later in twelve; difficult breathing initially in none but later in thirteen; painful extremities initially in three and later in nine; restlessness at night initially in two and later in eight; and abdominal pains initially in two and later in five.

The relation of objective symptoms appearing first as initial symptoms and then later after the onset of leucemia was as follows: enlarged lymph nodes were initial symptoms in fourteen cases and appeared later in forty-one; an enlarged spleen occurred initially in none but later in fifty-four; hemorrhages occurred initially in three and later in forty-

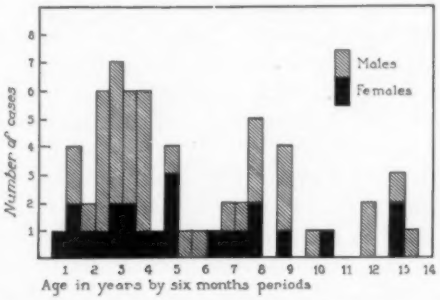

Chart 1.—Age and sex incidence of acute lymphatic leucemia.

seven; pallor initially in fifteen and later in thirty-five; and an enlarged liver initially in none but later in forty-nine.

It is often possible by examination of the blood to make a diagnosis of acute lymphatic leucemia in the presence of indefinite complaints, such as weakness, listlessness, anorexia, and irritability, before the appearance of the more classical symptoms of enlargement of the liver and spleen and hemorrhages in the skin and mucous membranes. Ordinarily, acute lymphatic leucemia in childhood runs a course lasting about ten weeks, and the diagnosis in most instances is not made until the disease has run more than half its course. Routine morphologic studies of the blood among patients with weakness, pallor, cachexia, unexplained fever, and enlargement of the lymph nodes will frequently establish the diagnosis early in the course of the disease.

Because of the relatively greater incidence of acute lymphatic leucemia in early childhood, at the time when the lymphatic structures of the body attain their greatest development and when the blood normally

contains a larger proportion of lymphocytes, the diagnosis of leucemia of the acute lymphatic type at times becomes exceedingly difficult. As the clinical features are not always characteristic, careful examination of the blood usually will assist one in making the diagnosis. The results of such studies of the blood in these sixty cases of acute lymphatic leucemia are reported here.

It might be well to say a word about the normal blood picture in infancy and childhood as it appears in the standard works on the subject.[6, 7, 8] At birth, values for hemoglobin, erythrocytes, and leucocytes are all above the normal figures for adults. This is attributed to the overactivity of the bone marrow which carries over from fetal life. By the Sahli method the hemoglobin content of the blood averages more than 100 per cent, until the age of two weeks, falls rapidly to 75 per cent at six months and stays there for the remainder of the first year. After this period, there is a gradual rise to an adult value of from 85 to 100 per cent, which is attained at sixteen years of age.

The erythrocyte count[8] at birth varies from 5,000,000 to 9,000,000 per cubic millimeter of blood; this value falls to 5,000,000 at the end of two weeks and then decreases gradually to between 4,000,000 and 5,000,000 per cubic millimeter at six months of age. From then on there is a gradual increase to the adult value of 5,000,000 per cubic millimeter at fifteen or sixteen years of age.

Leucocytes, according to Lippman,[7] average 16,000 per cubic millimeter of blood at birth, rise sharply to 22,000 at twelve hours, then fall rapidly to from 7,000 to 10,000 per cubic millimeter at five days. Washburn's[9] recent work emphasizes the marked variability of leucocyte counts among normal, healthy infants. There is a gradual rise to 10,000 per cubic millimeter which is maintained during the remainder of the first year; this is followed by a slight fall in the total number of leucocytes until the fourth year when an average of 9,000 per cubic millimeter is reached, in accordance with the figures of Perlin.[10] The number remains constant until the eighth year, then decreases gradually to adult figures at the sixteenth year. There is a normal physiologic variation in the total leucocyte count which is marked by an increase that takes place between 2 and 4 P.M. and a similar increase that takes place between these same hours in the early morning. This has been shown by Sabin,[11] as well as by Shaw,[12] to be due to an increase in neutrophiles in the peripheral circulation. As most of the blood counts in the present cases were done in the morning, variations due to physiologic changes largely are eliminated.

The differential leucocyte count indicates that the percentage of neutrophiles varies inversely with that of the lymphocytes.[6] The neutrophiles compose from 60 to 70 per cent of the total number of leucocytes at birth, decrease to a number equaling the lymphocytes at forty-eight hours, and continue to decrease to 30 per cent at the end of the

first week of life. At the age of five years, the percentage of neutrophiles again has risen to equal that of the lymphocytes and from then on always exceeds the latter. The age at which the adult neutrophile-lymphocyte ratio is reached is sixteen years. The lability of neutrophiles is notable. Their percentage of the total leucocyte count may vary from 38 to 61 in six hours.[7] The monocytes range from 7 to 10 per cent during the first year of life, but they thereafter decrease in number. The eosinophiles may comprise 6 per cent of the total number of leucocytes from the ages of three to five years but are fewer after that time. The platelet count is variable; if low at birth, it tends to rise, and vice versa. The usual number of platelets in the blood during infancy and childhood is between 200,000 and 300,000 per cubic millimeter by the direct method, using sodium citrate as the diluent and no stain.[13] The numerous variations in the methods of counting platelets, in which normal values range from 200,000 to 700,000 per cubic millimeter depending on the method employed, make such counts worthless unless the method used and its normal value are understood.

Immaturity in the erythrocytes and a shift to the left indicative of immaturity in the leucocytes are normally present the first few days after birth. Normoblasts are seen in decreasing numbers up to five days of age. Polychromatophilia and anisocytosis are normally found during the first two weeks of life. Metamyelocytes and a few myelocytes occur normally during the first week after birth. Immaturity of the leucocytes is readily produced by infection in infancy due to the lability of the bone marrow at this age. It is this factor which at times makes the diagnosis of leucemia among young children extremely difficult.

STUDIES OF THE BLOOD IN ACUTE LYMPHATIC LEUCEMIA

Secondary anemia was the rule, with low values for hemoglobin and for erythrocytes. Few other conditions in childhood present such a picture of severe and long-standing secondary anemia. In most cases, the concentration of hemoglobin was about 30 per cent by the Dare method, and erythrocytes numbered from 1,000,000 to 2,000,000 per cubic millimeter of blood. The presence of normoblasts, polychromatophilia, and anisocytosis usually was encountered. Absence of these features indicated a lack of regeneration of the erythrocytes and an aplastic type of blood picture. This is not uncommonly found in the terminal stage of acute leucemia.

Reviewing the leucocyte counts in this series of sixty cases of acute lymphatic leucemia, using a median value of 10,000 per cubic millimeter as the dividing line between a low and high leucocyte count, thirty-eight patients had counts whose median was greater than 10,000 per c.mm. The highest count in the group was 1,580,000 leucocytes per cubic millimeter. Four patients had leucocyte counts that ranged constantly near the

median of 10,000 per cubic millimeter. Eighteen had counts whose median value was less than this. Of fourteen selected patients studied over a long period, all but one had a median leucocyte value less than 10,000 per cubic millimeter (Table I). In only two cases did these values exceed 5,000 per cubic millimeter.

TABLE I

SEVERE SECONDARY ANEMIA AND LEUCOPENIA. MEDIAN VALUES IN FOURTEEN CASES OF ACUTE LYMPHATIC LEUCEMIA STUDIED OVER LONG PERIODS

CASE	HEMOGLOBIN, PER CENT	ERYTHROCYTES	LEUCOCYTES	LEUCOCYTE COUNTS. TOTAL NUMBER	LEUCOCYTE COUNTS HIGHER THAN 10,000 PER C.MM.
1	35	2,220,000	4,900	29	6
2	44	3,370,000	4,900	33	1
3	40	2,520,000	3,600	17	3
4	40	2,560,000	4,650	57	13
5	25	1,610,000	5,000	11	0
6	41	2,630,000	4,800	32	11
7	47	2,770,000	8,900	14	5
8	34	2,590,000	6,100	18	1
9	40	2,080,000	3,400	21	0
10	30	1,800,000	4,200	18	7
11	33	2,310,000	4,800	18	0
12	23	1,530,000	3,350	14	0
13	37	2,820,000	28,400	44	34*
14	26	1,660,000	4,100	14	0
				340	81

*If Case 13 is omitted, only 16 per cent of all the leucocyte counts in the remaining thirteen cases rose above 10,000 per cubic millimeter. In only two instances were the median leucocyte counts higher than 5,000.

It is to be noted that approximately a third of the sixty patients had a leucopenic phase at some time during the course of the condition. Eleven of these were followed for periods varying from three weeks to three and a half months. Daily counts were made in most cases in which it was demonstrated that the leucopenic phase was not transitory. In some cases leucocytosis which could not be attributed to infection was noted. It is possible that in some cases the disease may run its entire course with no leucocyte count above the normal range. It must also be stated that the cases characterized by normal or subnormal leucocyte values were not those in which patients were most actively treated with radiotherapy. They maintained a low leucocyte count for long intervals during which no treatment was given. The clinical aspect in these cases did not vary from that in the more usual type of case in which the leucocyte count was high. The presence of definitely immature leucocytes in the peripheral circulation established the diagnosis of acute lymphatic leucemia in every case when followed for a sufficiently long time. It seems worthy of repetition that the conception of acute lymphatic leucemia as a disease typified by an increase in the leucocyte count is erroneous, since a third of our cases failed to bear this out. A

physician must be on his guard not to pass over those cases in which the leucocyte counts are low or which present other features of leucemia. This may be avoided by repeated examination of the blood smears for immaturity in the leucocytes.

MORPHOLOGIC CHARACTERISTICS OF THE LEUCOCYTES IN ACUTE LYMPHATIC LEUCEMIA

The morphologic characteristics of the leucocytes were reviewed in six cases in which patients were followed for as long as three months; the blood smears were taken at short intervals and, in most cases, daily. Immaturity of the lymphocytes back to the stem cell could be demonstrated in every case. Since immature cells were not present in every smear, repeated examinations of the blood, taken at frequent intervals, often were necessary to discover their presence. In two cases it was noted that the type cell was approximately 12 microns in diameter, with a bluish rim of cytoplasm so small as to appear absent in some instances. On casual observation these cells could easily be mistaken for normal lymphocytes, but more careful inspection of the nucleus revealed that the chromatin was arranged in fine strands sharply demarcated from the parachromatin. Nucleoli were frequently seen in these nuclei. Occasionally an immature lymphocyte was seen with a stippled appearance of the nuclear chromatin in contrast to the more usual type cell with the stringlike arrangement of chromatin. The persistence of such immature cells in the blood in spite of their small size established the diagnosis of acute lymphatic leucemia.

By studying the blood smears for a long time in almost every case, it was possible to demonstrate the presence of lymphocytes with indented, notched, cleft, bisected, or lobulated nuclei. The more immature the cell, the greater the tendency to irregularity of the nuclear border. The outline of these cells is well illustrated in Fig. 1. In all these primitive cells the fine, sievelike arrangement of chromatin, distinct from the parachromatin, and the presence of nucleoli established the immaturity of the cell. The amount of cytoplasm of these cells was small; the cytoplasm was bluish gray with a clear perinuclear zone, and it contained azure granules that were very fine in all but one case. Such cells are probably to be classed as Rieder forms and have been well depicted in the work of Pappenheim,[14] Downey,[15] and, more recently, of Gittins.[16] The frequency with which this type of immature cell was encountered and its rather striking appearance seem worthy of emphasis.

Plasma cells were often found containing very dark cytoplasm with a round or oval nucleus, usually eccentric in position and filled with heavy, dark chromatin strands that almost completely covered the parachromatin. These cells were not a constant finding in any case in which they appeared, and their significance cannot be stated.

In several cases unusually small lymphocytes and neutrophiles with mature nuclei were noted, ranging from 5 to 7 microns in diameter. The granules in the cytoplasm of these neutrophiles were somewhat coarser

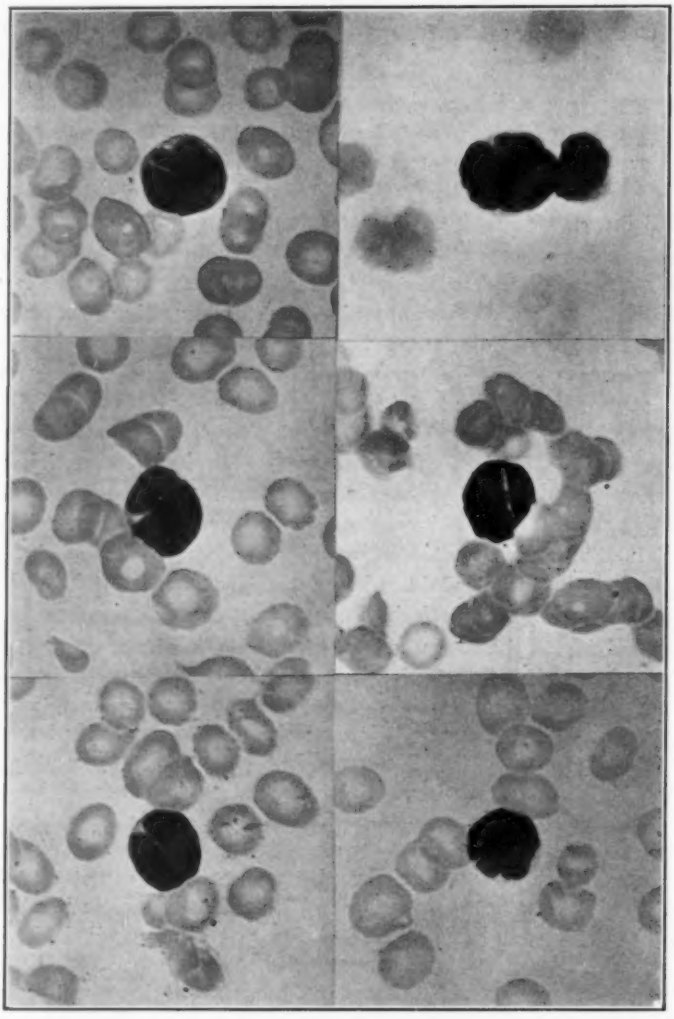

Fig. 1.—Immature lymphocytes with nuclear indentations seen in acute lymphatic leucemia. Variations in nuclear contour and narrow band of cytoplasm about nuclei may be seen (×1000).

than normal and their nuclei rather pyknotic. Such cells were taken as evidence of unusual activity of the bone marrow which poured out cells into the blood stream before they had ripened to mature sizes.

A shift to the left and the appearance of toxic changes in the polymorphonuclear neutrophiles were not uncommon. Immaturity often occurred in both myeloid and lymphatic series at alternating periods, so that it was necessary to follow the blood smears over extended periods to determine in which series the immaturity predominated. The lability of the bone marrow in childhood may account for this finding. A lessened degree of immaturity appeared to parallel the subjective improvement of the patient.

The toxic neutrophile was frequently seen and was characterized by the dark, pyknotic nature of the nuclear chromatin, which was irregular in distribution. The neutrophilic granules in the cytoplasm varied greatly in size, shape, and in staining intensity, tending to be coarser than usual and more angular than round. Vacuoles not uncommonly occurred in the cytoplasm, and the cell border was often irregular and ill defined. The immature lymphocytes showed vacuolization and fragmentation very frequently.

The erythrocytes exhibited the usual picture of secondary anemia with anisocytosis, polychromatophilia, and the presence of reticulocytes and normoblasts, indicating good regeneration of the erythrocytes. An aplastic blood picture was not encountered in the cases in this series.

The platelet counts by the citrate method were uniformly low in all instances in which they were made. This finding has been noted in the literature and, in the chronic form of the disease, has been used by some as a differential point to distinguish lymphatic leucemia from the myelogenous type, since the latter is usually accompanied by an increase in platelets. It has been stated by Minot and Buckman[17] that an increase in the blood platelets is indicative of improvement.

EFFECTS OF BLOOD TRANSFUSION

After transfusion of blood, the values for hemoglobin rose rapidly, the erythrocyte count less rapidly. Whereas the value for hemoglobin in some cases rose the day following transfusion, the erythrocyte count did not attain its maximal increase until the third day after this procedure. The effects of transfusion on the leucocytes were threefold: first, the total count tended to return to normal, that is, if it had been high there was a decrease and if low, a rise. The maximal effect was noted from three to five days after transfusion. Second, the degree of immaturity of the leucocytes became less, and third, the normal ratio of neutrophiles to lymphocytes was restored. Subjective improvement was the usual accompaniment of these changes.

EFFECT OF RADIUM AND ROENTGEN THERAPY

Treatment with radium and roentgen rays causes a more rapid and pronounced fall in the number of leucocytes in the circulating blood when their numbers are greater than normal. Minot and Spurling[18]

found an elevation of the leucocyte count and of the number of neutrophiles in the first twenty-four hours following treatment with roentgen rays of a leucemic patient. Following this, there was a decrease in the leucocyte count and in the neutrophile count which reached their lowest values six days after treatment. A slight decrease in values for hemoglobin and erythrocytes follows the use of radiotherapy. The lymphocytes are reduced in number more rapidly than are the neutrophiles, so that a relative polymorphonuclear neutrophile leucocytosis results. Radiotherapy has a more lasting effect than transfusion but is less marked with each repetition. Following this procedure, too, a sense of well-being is restored.

EFFECT OF INTERCURRENT INFECTIONS

Intercurrent infections had no constant effect on the leucocyte level, nor was there an increase in the number of neutrophiles in the four cases in which infection occurred and in which blood smears were studied. In two cases there was a rise in the total leucocyte count, but no accompanying increase in neutrophiles. In one case a definite increase in immaturity of the leucocytes occurred as a result of intercurrent infection.

TERMINAL LEUCOCYTE COUNTS

The leucocyte counts at death were followed in sixteen cases in which records were made within the last three days of life. In only one case was there a terminal rise, which may be explained as the last burst of activity of the overtaxed bone marrow. The other fifteen patients had leucocyte counts which remained at their previous level or showed a terminal decrease. In eight cases transfusions or radiotherapy within the last three days of life might be considered causative factors in the terminal fall in the leucocyte counts where previous levels had been elevated. There was no tendency noted toward terminal increase in leucocytes, in seven cases in which leucocyte counts were low, with the possible exception of the first case cited. In fact, the converse was more generally true, and it indicated exhaustion of the hematopoietic depots as death approached.

SUMMARY

Acute lymphatic leucemia, although rare, is a disease that occurs not infrequently in childhood, especially in the first four years of life. The condition predominates among males in all age groups, especially affecting those in the youngest age group. In approximately a third of the cases, the leucocyte count is less than 10,000 per cubic millimeter of blood. A high leucocyte count is not necessary to make the diagnosis. Marked secondary anemia usually is present. The most reliable diagnostic finding is the repeated observation of immaturity in the lymphocytes back to the stem cell. Morphologic findings of frequent occurrence

in the blood smears in cases of acute lymphatic leucemia are stem cells, of unusually small diameter, Rieder forms, plasma cells and toxic neutrophiles. The effects of transfusion, radiotherapy, and intercurrent infection on the blood are noted. The terminal leucocyte counts tend to be low. It would be possible to make the diagnosis earlier in more cases if routine morphologic examinations of the blood were made.

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LOW CALCIUM TETANY OF THE NEWBORN

Review of the Recent Literature and Report of Another Proved Case

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CASES of low calcium tetany in the newborn are being reported in the literature with increasing frequency. Recently, the author[1] described a case of tetany of the newborn which he had observed over a year ago. Hyperpyrexia had been present from birth, and twitches and convulsions had appeared on the thirteenth and seventeenth days of life. The blood calcium concentration had been 7.4 mg. In this report mention was made of only three prior reports in the literature of proved cases of low calcium tetany occurring within the first three weeks of life (Shannon's third case,[2] Bass and Karelitz' first case,[3] and Maslow's third case[4]). Unfortunately, reports by Nesbit[5] and Sincock[6] had been overlooked. Nevertheless, of the six cases comprising Nesbit's report, only the first case had a sufficiently lowered calcium concentration (8 mg.) to be included in the above list of proved cases of low calcium tetany of the newborn. In Sincock's two cases the blood calcium concentrations were 7.0 and 6.0 mg., respectively, in the presence of marked hypertonia of the muscles of the extremities, positive Chvostek phenomena, and a 4 milliampere cathodal opening contraction to the galvanic current. In addition, in his second case projectile vomiting and hyperpyrexia occurred.

Several other reports have appeared in the literature since the preparation of the author's first paper. In June, 1933, Small[7] reported the onset of twitchings of the face and of the extremities in a nine-day-old infant with a convulsive seizure on the eleventh day. On the sixteenth day of life, a week after the onset of symptoms, the calcium content of the blood was determined for the first time and found to be 5.6 mg. per hundred cubic centimeters of serum. Calcium chloride was given orally with resultant cure. The Chvostek and Trousseau phenomena were negative, and no laryngospasm was noted.

In September, 1933, Guild[8] described the appearance in a two-day-old infant of spastic seizures accompanied by laryngeal stridor, cyanosis, and positive Chvostek and peroneal phenomena. Although the spinal fluid calcium content was found to be 3.9 mg. per cent, the blood calcium content was not determined. Since the spinal fluid calcium is approximately 45 per cent of the blood calcium, the corresponding blood calcium would probably be 9 mg. Therefore, although the case is reported

under the title of "Tetany of the Newborn," it is not a proved one. The author herself states: "The most we can say is that we cannot prove its absence, especially since the spinal fluid calcium was somewhat low, though I do not believe that the baby had tetany." Guild also quotes the history of a ten-day-old infant (Case 3 on p. 50 of her report) who had had severe diarrhea for three days followed by twitchings of the face and arms for several days with a blood calcium content of 6 mg. per cent and a phosphorus of 9.5 mg. per cent. However, examination of the spinal fluid revealed a definite xanthochromic discoloration, and the symptoms did not yield to calcium therapy. An overdose of parathormone resulted in a rise of the blood calcium and phosphorus levels at the time of death to 20 mg. and 15 mg., respectively. At necropsy normal parathyroids and a large intracranial hemorrhage were found. The absence of other hemorrhages, particularly of intestinal hemorrhages, was interpreted as pointing against the overdose of parathormone having been the cause of death. Apparently the case was one of tetany combined with an intracranial hemorrhage. The persistence of symptoms in spite of calcium therapy was probably due to the intracranial hemorrhage.

Shortly thereafter Bloxsom and Nicholas[9] described two cases of twitching occurring during the first day of life. Since the calcium content was not determined in their first case, the case remains unproved. Although the blood calcium content was relatively normal (9.2 mg.) in their second case, the ionizable calcium concentration was low.

In February, 1934, Craig,[10] reported an authentic case of low calcium tetany in a newborn infant. Generalized convulsions and facial twitchings occurred from the ninth to the fifteenth day. A diagnosis of cerebral hemorrhage was made. On the sixteenth day, the calcium and phosphorus concentrations were 7.3 mg. and 4.4 mg., respectively. Oral calcium therapy was given, but the convulsions continued (52 and 33 seizures on the seventeenth and eighteenth days, respectively). Following an intramuscular injection of calcium on the eighteenth day, the symptoms promptly ceased. Although the Chvostek phenomenon had been positive, carpopedal spasm and laryngospasm were not present at any time during the illness.

Gaberman[11] is quoted by Bass to have found a blood calcium concentration of 5.3 mg. in a newborn infant with vomiting, hyperpyrexia, and convulsions. This case has not been reported to date.

The increasing frequency of occurrence of these cases of low calcium tetany of the newborn surely cannot be due to an increasing incidence of the syndrome. It is more likely that the pediatrician has been made aware of the existence of the disease in the newborn by the report of the early cases mentioned previously. He is now alert for any clinical manifestations of tetany and realizes the necessity for determining the cal-

cium content of the blood in any case of twitches or convulsions of unexplained etiology in the newborn. It is likely that a fair proportion of the cases of convulsions in newborn infants which terminated fatally in the past and were diagnosed as so-called "cerebral injuries" actually may have been unsuspected cases of low calcium tetany in the newborn.

A second proved case of low calcium tetany has been observed by the author within a period of fifteen months.

Baby K., a male infant, weighing 6 pounds 12 ounces, was delivered by means of low forceps by Dr. Hellman at the Lenox Hill Hospital. At the time of delivery, the infant's oral and nasal passages were filled with meconium which was removed digitally. The infant was somewhat cyanotic, crying feebly from time to time. The temperature was subnormal (97.2° F.). Toward the end of his first day of life, the temperature rose to 103.8° F., and the respiratory rate rose to 75 per minute. Physical examination revealed the presence of labored respiration, dilatation of the alae nasi, cyanosis of the lips and of the nail beds of the fingers and the toes, and dullness with crepitant râles at the left base. A positive Chvostek phenomenon was elicited. A diagnosis was made of a pneumonia secondary to the aspiration of meconium at birth. CO_2 and oxygen were administered in an oxygen tent; the color improved; and the respirations became less labored. After ranging between 102° and 103° F. for thirty-six hours, the temperature fell to normal on the third day. During the febrile stage, fluid was supplied by clyses, and an intramuscular injection of paternal whole blood (50 c.c.) was given toward the end of the second day. Several hours later, slight transient twitches of the facial and extremital muscles were observed but did not again recur during the course of the pneumonia. The Moro test was negative for any evidence of cerebral injury. The chest signs gradually cleared. The respiratory rate remained elevated although the respirations seemed less labored, and the temperature remained normal.

A formula consisting of evaporated milk, water, and dextrimaltose was well taken and the infant, after having gained initially as a result of the retention of the fluid given by clysis, continued to gain in weight. On the fifth day a second intramuscular injection of paternal whole blood (30 c.c.) was given and was well absorbed. The infant seemed completely well.

Suddenly at the end of his seventh day of life, twitchings of the legs, arms, and eyelids were noted, lasting for several minutes and being accompanied by a slight degree of cyanosis. Following this, the infant slept well and took his feedings eagerly. On physical examination the fontanel was not bulging; the reflexes were normal, but the Chvostek sign was still positive. The reaction to the Moro test was again normal in character.

Eight hours later, on the eighth day of life, twitchings of the arms and legs were again noted lasting for about half a minute, being followed by a generalized convulsion lasting for three minutes. Physical examination revealed a normal Moro phenomenon but, although a much more positive Chvostek reaction was elicited, no carpopedal spasm or laryngospasm was present; the chest was clear, but a thin purulent discharge was observed in the right ear canal. A tentative diagnosis of low calcium tetany of the newborn secondary to the pneumonia and the subsequent acute right otitis media was made. A specimen of blood was taken for chemical analysis and 10 c.c. of calcium gluconate (10 per cent solution) were given intravenously through the same needle. The calcium content of the blood was found to be 7.6 mg. per 100 c.c. of serum. (The phosphorus content was not determined because of an insufficiency of serum in the specimen sent for the determination.)

Thereupon one ampule of calcium gluconate (10 c.c. of a 10 per cent solution) was given intravenously each day. Calcium gluconate and viosterol in increasing doses were given orally. Two injections of the calcium gluconate were given intramuscularly during the first two days of therapy.

No more twitchings or convulsions were observed until the eleventh day of life (on the third day of calcium therapy), when twitching of the facial muscles for a duration of two minutes was noted. The intravenous and the oral therapy were continued throughout the second and third weeks, for a second blood determination done on the fifteenth day of life (on the eighth day of therapy) revealed a blood calcium and phosphorus content of 7.5 mg. each per hundred cubic centimeters of serum. The general condition continued to improve, and the infant gained in weight although the thin purulent aural discharge persisted without a febrile reaction. The Chvostek phenomenon remained positive until the end of the second week of life. Carpopedal spasm and laryngospasm were not observed at any time during the illness.

The intravenous therapy was discontinued after fourteen daily injections had been given, but the oral administration of calcium gluconate (45 grains per day) and of viosterol (30 drops per day) was continued. A third blood calcium determination seventeen days after the institution of calcium therapy revealed a blood calcium content of 9.3 mg. per 100 c.c. of serum. The infant was discharged three days later at the age of three weeks after a gain of 2 pounds and 5 ounces over its birth weight. Save for the discharge from the right ear which had lessened, physical examination showed him completely normal. The mother was instructed to continue the daily oral administration of calcium gluconate and viosterol for several weeks to ensure the nonrecurrence of symptoms of tetany.

COMMENT

The only signs or symptoms of tetany present in this patient were the positive Chvostek phenomenon present from birth and the twitchings and convulsions occurring on the seventh and eighth days. Laryngospasm, carpopedal spasm, and subcutaneous edema were not present at any time during the course of illness.

This case serves to emphasize the fact that laryngospasm and carpopedal spasm, which are ordinarily considered cardinal signs of tetany, need not necessarily form part of the symptom-complex. The presence of the positive Chvostek phenomenon had not been regarded as significant prior to the development of the twitches and convulsions, for this sign is observed frequently in healthy newborn infants who have normal blood calcium concentrations and do not manifest clinical symptoms of tetany (Stevenson, Mitchell and Koch[12]). The transient twitching of the face, first noted on the second day of life during the course of the pneumonia, must have been the first symptom of active tetany although its significance was not recognized at the time. The twitchings of the muscles of the face and extremities followed by convulsions noted on the seventh day were recognized as manifestations of active tetany, and treatment was instituted promptly.

It is of interest to note that the presumptive diagnosis of tetany of the newborn had been made and intravenous treatment begun prior to the analysis of the specimen of blood for its calcium content. The di-

agnosis was based on two factors: first, the absence of any signs pointing toward cerebral injury or meningeal involvement such as an abnormal response to the Moro test, bulging of the anterior fontanel, or the changes in the reflexes noted in meningeal irritation; second, the presence of unexplained twitchings and convulsions occurring during the course of infection in a newborn (the aspiration pneumonia and the purulent otitis media).

Infection may precipitate the development of symptoms of tetany in an older infant, and that this occurs in cases of latent infantile tetany (low calcium concentrations without active symptoms) is well recognized. Similarly, in the newborn latent tetany can exist as is shown by Stevenson, Mitchell, and Koch's[12] case of a normal newborn infant with 7.3 mg. of calcium but without clinical symptoms. It would seem possible likewise in the newborn for an infection in such an infant to cause a precipitation from the latent stage (without clinical symptoms) into an active or manifest tetany; so that presumably, in the case quoted herein, the blood calcium may have been low at birth, and a latent form of tetany may thus have been present only to have symptoms occur as a result of the infection.

Certainly in the case of low calcium tetany reported herein, the diagnosis might have been completely overlooked in the absence of other symptoms (laryngospasm or carpopedal spasm) if the rôle of infection in precipitating symptoms of active tetany had not been so visualized. Had one waited for the development of such suggestive signs as laryngospasm or carpopedal spasm before venturing the diagnosis of tetany and applying the proper therapy, the outcome might have been fatal. This case emphasizes the necessity for blood calcium determinations in all cases of convulsions or twitches in the newborn of unexplained etiology, even in the absence of other confirmatory evidence of tetany (laryngospasm, carpopedal spasm).

Another point of interest is that the blood calcium content remained relatively unchanged after the first week of intensive calcium therapy even though the infant was symptom-free after the third day of therapy. It was not until the end of the second week of therapy (after fourteen daily intravenous injections of 10 c.c. of the 10 per cent solution of calcium gluconate) that the calcium concentration in the blood reached the level of 9.3 mg. Even then, to prevent recurrence of symptoms from a subsequent lowering of the calcium content of the blood such as occurred in Powers'[13] case, oral calcium and viosterol medication was continued for three weeks after the baby's discharge from the hospital.

SUMMARY

1. A case of low calcium tetany in a newborn infant is reported. Facial twitchings first occurred on the second day of life during the course of aspiration pneumonia. Twitchings recurred on the seventh

day of life and again on the eighth day, followed by convulsion. The blood calcium content was 7.6 mg. Intensive therapy was instituted. Although symptoms of active tetany ceased after the third day of therapy, the blood calcium content was relatively unchanged (7.5 mg.) at the end of a week of therapy and was raised to 9.3 mg. only after two weeks of intensive intravenous and oral calcium therapy. Vitamin D in the form of viosterol was given to increase the absorption of calcium through the intestinal tract.

2. This is the second proved case of low calcium tetany in the newborn during the first three weeks of life observed by the author within a period of fifteen months.

3. The presence or absence of the Chvostek phenomenon is not of diagnostic significance. Although laryngospasm and carpopedal spasm may be present, they must not necessarily form part of the symptom-complex. The occurrence of convulsions or twitchings of unexplained etiology in a newborn infant, even in the absence of other signs and symptoms of tetany, necessitates a blood calcium determination to establish or rule out low calcium tetany.

5. The increasing frequency of reports of low calcium tetany in the newborn is obviously not due to an increased incidence of the syndrome but rather to increased watchfulness on the part of the physician and routine blood calcium determinations in cases of convulsions or twitches of unexplained etiology in the newborn.

6. If the calcium content of the blood were determined routinely in all such infants, it is probable that low calcium tetany would be found much more commonly in the newborn period than has hitherto been the case.

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HEMIHYPERTROPHY

Report of Four Cases

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THE literature on hemihypertrophy is accumulating, but very few studies have been made outside of the work of Gesell[1] who reports the material up to 1921. He considers the condition the result of some developmental disturbance dating back to an early embryonic stage and also as "a form of asymmetrical twinning due to a possible deviation in the normal process of twinning."

The majority of cases occur in males; the right side is usually involved; nevi may or may not be present. The mentality in some patients is abnormal; in others it seems to be normal. Three of our patients are apparently normal; one is definitely abnormal.

The sebaceous glands in some instances on the affected side seem to have an abnormal secretion; the sweat glands are abnormally active; the growth of hair is thicker; the nails grow more rapidly; and also there is an earlier eruption of teeth. The temperature on the affected side is reported to be one or two degrees higher than on the other.

Some patients have an extreme enlargement of the fingers or toes on the affected side as the only abnormal hypertrophy.

Pathology.—There is a unilateral hypertrophy of the soft structures, the bones, and occasionally of the internal organs, with the pituitary and sella turcica usually normal. In the literature some of the patients are stated to look older on the affected side than on the other. The half of the brain opposite to the affected side has been reported as enlarged or hypertrophied. *Microscopic examination* shows that there is an increase in the interstitial connective tissue and in the tissue of the peripheral nerves.

Differential diagnosis from hemiatrophy is not difficult as there is no atrophy present.

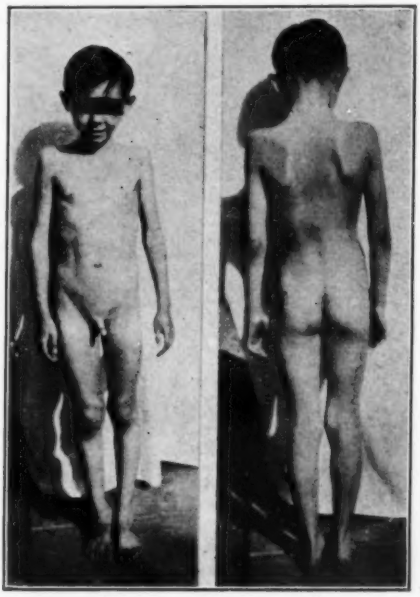
The prognosis is good.

The method of treatment is usually determined according to the parts affected. For some, orthopedic appliances are helpful, and in some cases, such as certain face abnormalities, operative interference is indicated.

From the California Babies' Hospital and the Pediatric Department of the California Hospital.

In our search of the literature no case of congenital hemihypertrophy is recorded, some authors going so far as to state the condition is not hereditary. Our cases of mother and daughter are therefore unusual.

CASE 1.—D. B. was first seen Mar. 3, 1932, at the age of nine years and one month. He was the first child, delivered by forceps at the seventh month of gestation. His birth weight, 6 pounds 8 ounces, does not correspond to the gestation period. He was breast fed for two months, then artificially fed. He was given cod liver oil and orange juice and some heliotherapy. The first tooth erupted at the sixth month, and he was walking and talking (?) at the end of the first year. He has had measles, pertussis, frequent colds, and a tonsillectomy in 1930. Parental history is unim-



A. *B.*

FIG. 1.—Case 1. D. B. *A.* Note difference in size of legs. *B.* Note scoliosis.

portant for the condition under consideration. When seen he complained of frequent colds and a tendency to wheezing. The physical asymmetry was noted on examination, and the mother stated that when the lad was four years old he had an injury over the left mastoid, at which time the difference in the legs was noted.

Physical examination shows the right hip, leg, and foot slightly larger than the left. A compensatory scoliosis to the left is marked.

The measurements of the shoulder	Right arm	Left arm
to tip ulnar process	43.7 cm.	43.2 cm.
Palm of hand circumference	15.5 cm.	14.5 cm.
Ant. Sup. spine ileum to inner	Right leg	Left leg
malleolus	69.0 cm.	68.5 cm.

Right thigh is 1 cm. larger than the left.

The right calf of the leg is 1 cm. larger than the left.

He wears a size larger shoe on the right foot than on the left.

He was referred to Dr. H. W. Spiers for orthopedic consultation and his report shows "a marked difference in size and length of the left side, from the pelvis downward, as compared with the right. There is a slight beginning structural scoliosis. X-ray films were made of the pelvis, spine, knees, hands, and feet. They show changes in size and shape of the left pelvis, left thigh, and left foot. It is noted throughout that there is some delay in ossification of the smaller bones, particularly in the hands."

A. *B.*

Fig 2.—Case 2. J. B. May, 1934. Hemihypertrophy and congenital heart disease. (The distance between the lines is 5 inches.)

Corrective shoeing and exercises were prescribed.

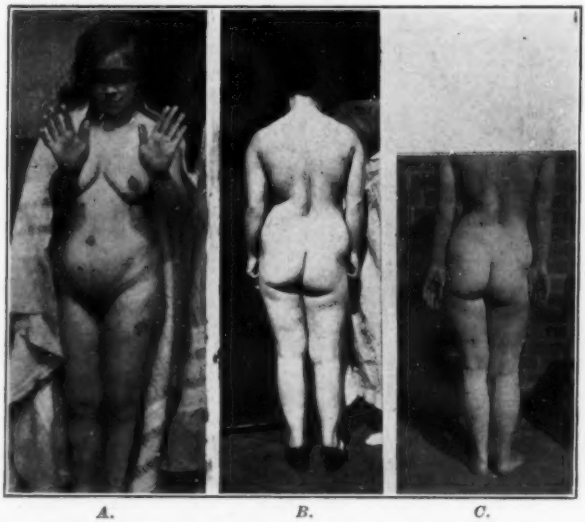
Mentally this boy is normal for his age.

CASE 2.—J. B., aged nine months, came to the Anita Baldwin Clinic Dec. 28, 1931. She was the second child, delivered normally, but not breast fed. Birth weight was 6 pounds 4 ounces. The older child, a girl, is normal physically and mentally. The family history is irrelevant except for the mother whose history is detailed in the next report.

On physical examination, a small nevus 1 cm. in diameter was found on the right shoulder. The musculature was fair, but the infant could not sit alone. The anterior fontanel was small; the sagittal suture, open from the glabella to the posterior fontanel. The left side of the skull looked smaller than the right, the left arm and leg shorter than the right side. The left middle and ring fingers were flexed and could not be extended.

The back of the head was flattened, and the fingers and toes clubbed. The lips were cyanotic. When the child cried, the skin was darkened.

The mother stated that the infant did not use her left arm until she was four months old. At birth the left leg was extended upward on the abdomen. At the present time she did not extend the left leg fully. Talipes valgus of the left foot was present. The left hand could not be completely supinated, and the left ear protruded more than the right.



A. *B.* *C.*

Fig. 3.—Case 3. Mrs. B. *A*. The tilted head shows the slight difference between the sides of the face. The hands show the difference to a slight extent. *B* and *C*. Posteriorly the scoliosis is marked, as is the leg length. The difference in circumference was not noted except by measurements.

The lungs and abdomen presented no abnormalities, but the heart had a harsh basal systolic murmur most pronounced to the left of the sternum, the murmur being transmitted in all directions—probably pulmonary stenosis. The reflexes were not especially active, though present.

Under treatment she improved so that when seen Mar. 21, 1932, at the age of one year, she could sit alone and had five teeth. The roentgenograms at this period showed normal epiphyseal growth for her age, equal on both sides for arms and legs. The blood Wassermann reaction was negative.

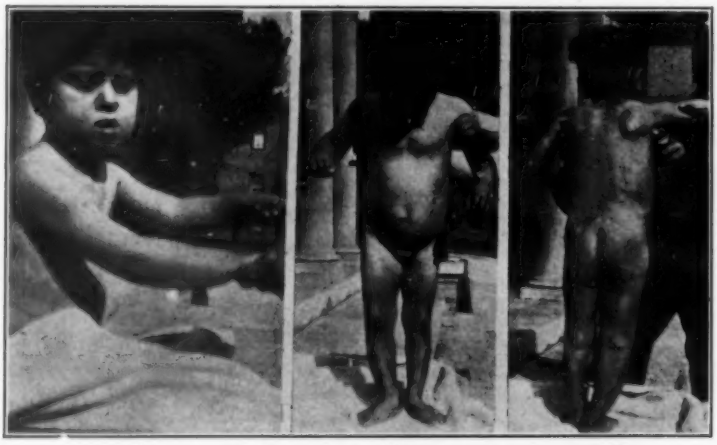
Dr. H. W. Spiers examined the infant July 27, 1932, and reported: "The infant is right-handed. The left arm is approximately ½ inch shorter than the right; the left leg is ⅜ inch shorter than the right. The circumference of the left calf of the leg is ⅛ inch less than the right, while that of the left thigh is ¼ inch less than

the right. The left leg is bowed below the knee, and the foot is in talipes valgus. Asymmetry of the face is evident. The roentgenograms confirm the clinical findings though no congenital variation was found except in size."

CASE 3.—Mrs. B., the mother of J. B., was born in June, 1905, hence at the time of her visit was twenty-six and one-half years old. Her birth weight was 6½ pounds; delivery was normal; and she was breast fed. When she was nine years old, a slight limp was noticed; this was very marked when she was sixteen years old. She menstruated first at the age of fifteen years. There was no record of a similar condition on either side of her family. She was the second child of four, the others being normal. She cut her first tooth at six months and walked at 15 months. The blood Wassermann reaction was negative.

Dr. H. W. Spiers reported the results of the examination:

"The left leg is 1½ inches longer than the right, the left calf of the leg ½ inch larger than the right; the left thigh is the same as the right. The arm circumference



A. *B.* *C.*

Fig. 4.—Case 4. M. G. *A*. Facial expression showing mental weakness. *B* and *C*. Anterior and posterior views showing difference in legs.

is about the same. There is slight facial asymmetry, the left side being wider and fuller than the right. The spine shows a marked degree of structural scoliosis."

CASE 4.—M. G., female, aged five months, entered the clinic June 23, 1928. The father was sixty years old; mother, thirty-eight years old. There were three other children living and well. The child was born at full term, weighing nine pounds, and was breast fed. Her disposition was reported as good, and she slept well. Bowel movements were regular.

On physical examination the right side of the body, face, and extremities were all noted to be larger than the left.

In January, 1929, when she was eleven months old, roentgenograms were made (Dr. Snure).

The film of the lower half of the body showed no difference in osseous structures; the femur at lower end on right side appeared larger because it was raised slightly from the film. Soft tissues appeared to be about 50 per cent increased in size. The

film of the upper half of the body showed an enlarged distorted heart shadow, probably a combination of several heart lesions. Density in the upper mediastinum was increased—probably heart and large vessels instead of thymus. The trachea was displaced toward the right. Right humerus appeared slightly larger than the left.

Only three ossification centers were present in the left wrist as against five in the right wrist; when carpal bones alone are considered, the left wrist would suggest an age of slightly less than two years. The right suggests an age period of about four years.

A roentgenogram of the whole body by Dr. K. S. Davis, of St. Vincent's Hospital, in April, 1929, showed a marked difference in the two sides of the body, especially in the extremities, the left arm being 50 per cent smaller than the right and the left leg showing about the same difference in size. There was noted the presence of five carpal bones in the right wrist and only three in the left wrist. There were six well-developed tarsal bones in the right ankle and the same number in the left ankle, but not as well developed as in the right. The left tibia and fibula were shorter and narrower than the right. The left femur was the size of the right. The left radius and ulna were considerably smaller than the right. The left humerus was smaller and shorter than the right, and its epiphysis not as well developed or as distinct as the right. The skull showed but little difference in the two sides on the basis of the roentgenographic findings.

Another roentgenogram in January, 1931, by Dr. Snure showed that the heart outline varied from normal in that the outline was extended about 1 cm. more than average from the aortic arch on the left side halfway down to the left apex. Whether this was an enlargement of the left auricle or pulmonary artery could not be determined.

The size of the left arm appeared to be 50 per cent that of the right. The same number of epiphyses were present in each wrist, but those in the right were 50 per cent larger than the left. The ossification center for the proximal epiphyses of the radius was distinct on the right side and absent or questionable on the left. Knee joints, except for size, showed no variation, the right being 50 per cent larger than the left. The left leg was 2½ cm. shorter than the right. Single anteroposterior film of the pelvis showed the right side longer and larger than the left.

No orthopedic treatment was recommended by the orthopedist as the mental condition of the child prevented cooperation. The blood Wassermann reaction was negative.

During the time she was under observation in the clinic, she was given cod liver oil and had an attack of pertussis from which she made a complete recovery. In March, 1929, she was given thyroid gland substance, 1 grain daily, which was continued to November of the same year but with no apparent effect on the mental or physical condition.

The child was subject to violent attacks of screaming; she would throw herself about, and it was with difficulty that the attendants could keep her from doing injury to herself. She was a low type of imbecile, mentally unresponsive to any person.

SUMMARY

Four cases of hemihypertrophy are presented, two being in mother and daughter. One subject is male, the others female. Three apparently are mentally normal; one, abnormal; one patient has a nevus, the others none. The right side is involved in the male and two females, and the left in one female.

No abnormalities, such as any excessive sweating, sebaceous secretions, hairy growth, or nail hypertrophy that are mentioned by some authors, were noted. One female infant had in addition a congenital cardiac lesion.

The treatment is essentially orthopedic to balance the body structure.

CONCLUSIONS

Hemihypertrophy is not as uncommon as has been suspected. The careful physical examination of all infants and children should reveal the condition if it is present. The statement that the condition is not hereditary cannot be proved, as we report a mother and daughter with the same complaint. There is nothing abnormal in the epiphyseal centers of these patients, so far as the roentgenograms show. The exact etiology has not been determined, but it is something in the early embryonic stage of development.

References, since the report of Gesell in 1921, are appended for anyone interested in details of all the reported cases.

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STRAMONIUM POISONING

A Review of the Literature and Report of Two Cases

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REPORTS of cases of poisoning in children from the ingestion of stramonium seeds are relatively uncommon, despite the prevalence of the Jimson weed.

Jimson weed, or as it is often called, Jamestown weed or thorn apple, is known to botanists as *Datura stramonium*, a species of the Solanacea or nightshade family to which also belong the red pepper, tobacco, tomato, belladonna, and bittersweet plants. It is a rank-scented, tall, much branched, narcotic, annual herb attaining a height of from three to six feet with five-lobed trumpet shaped flowers, and broad ovate shallowly lobed leaves. The fruit is a four-celled spinous capsule containing many small black-brown reniform seeds which measure approximately three by two millimeters. The plant flowers in late spring and the fruit ripens in early fall.

The leaves and seeds of the Datura contain hyoscyamine, atropine, and scopolamine in varying amounts. In some analyses, as much as 0.33 per cent of the alkaloid, atropine, has been found in the seeds and about 0.2 per cent in the leaves.

A perusal of the early literature indicates that the hypnotic and narcotic effects of members of the Datura species were known to the ancients. The capacity of the plant for causing forgetfulness and for rendering victims susceptible to suggestions is recounted in the *Iliad*, which describes the activities of Ulysses' men after they had drunk of Circe's drugged wine.

Shakespeare[16a, b] in *Romeo and Juliet* alludes to the mandragora as the potion which the holy friar gave to Juliet to make her appear dead. In *Antony and Cleopatra*, this was the powder that Cleopatra begged of Charmian that she might sleep out the gap of time when Antony was away.

The origin of the name "Jamestown weed," which is applied to the variety of Datura native to this country, dates back to the year 1676, when a group of men under Captain John Smith was sent to Jamestown, Va., to quell the Bacon rebellion. For comparison with the cases here reported it is interesting to note the effect of the ingestion of the leaves of the plant on these men, as recorded by Beverly:[1a, b]

From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospitals, Boston.

This being an early Plant, was gather'd very young for a boil'd salad, by some of the Soldiers sent thither, to pacifie the troubles of Bacon; and some of them ate plentifully of it, the Effect of which was a very pleasant Comedy; for they turn'd natural Fools upon it for several Days. One would blow a Feather in the Air; another would dart Straws at it with much Fury; and another stark naked was sitting up in a Corner, like a Monkey grinning and making Mows at them; a Fourth would fondly kiss and paw his Companions, and snear in their Faces, with a Countenance more antik than any in a Dutch Droll. In this frantik Condition they were confined, lest they in their Folly should destroy themselves; though it was observed that all their Actions were full of Innocence and Good Nature. Indeed, they were not very cleanly; for they would have wallow'd in

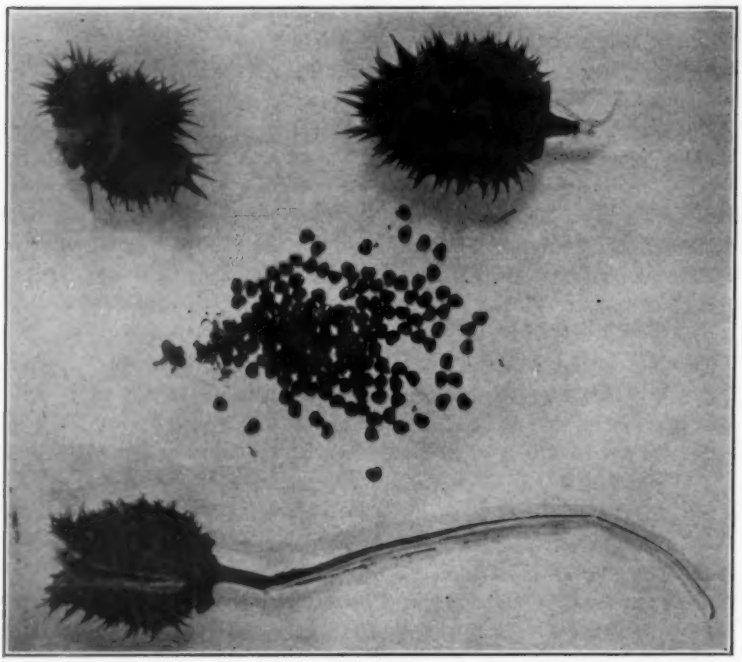

Fig. 1.—Full size reproduction of fruit showing spiny pod with reniform seeds.

their own Excrements, if they had not been prevented. A Thousand such simple Tricks they play'd, and after Eleven Days, return'd themselves again, not remembring anything that had pass'd.

Undoubtedly, it was this same drug that was used by the Algonquins and other tribes of Indians in their huskanawing ceremony for the initiation of their boys into the dignity of manhood as described by Beverly.[1b]

The Pueblo Indians of Mexico used the ground seeds of the Nacazcul (a South American variety of the *Datura stramonium*) mixed with pitch, because of the analgesic properties of the preparation, for setting

bones and dislocations. Warning was given, interestingly enough, against the use of excessive amounts of the powder, lest the patient be seized with madness and become the victim of "various and vain imaginations."

In the more recent literature, cases of stramonium poisoning have been reported from various parts of the world. Garvin and Ruh[3] describe an outbreak of poisoning among thirty boys in an orphanage with resultant pandemonium. The Jimson weed was later found in the play yard. Watt[19] and Breyer-Brandwyk report an outbreak of stramonium poisoning among forty-eight mine boys in Southwest Africa. These patients had eaten cooked beans containing the seeds of the stramonium plant which grows wild in that area, the contaminating seeds having been harvested unnoticed with the bean crop. Ismael[8] also describes cases of poisoning from gruel in which the seeds had been harvested with wheat. Additional cases of poisoning in children have been reported by Wilcox[20] and Grinnon[5] in the United States, by Howle[6] and Parkinson[15] in Australia; by Estapé and Bloise[2] in Uruguay, by Neyron[13] in France, by van Ravenswaay[18] in Netherlands, and by Mukopadhya[12] in India.

At the Kasr-el-Ainy government hospital at Cairo, according to Ismael,[8] datura poisoning ranks second in frequency to acute alcoholic intoxication among those brought into the hospital in an unconscious state. In Egypt and India datura seeds or their powder are added to food or beverages to facilitate robbery, or for homicidal purposes. Lenoir[10] describes the use of this drug among the inmates of the convict prison at New Caledonia. He reports that those given the drug usually become possessed of an idea to protect their hoard and that they usually run to the hiding place, unearth it, and thus facilitate robbery.

Another case of poisoning has been reported by Shoemaker,[17] from Philadelphia. He described the case of a twenty-six-year-old negro laborer who drank an infusion of the leaves from the Jimson weed as spring tonic.

The Jimson weed is very common throughout the United States and tropical regions of the Old World. During the summer and fall, small children playing in the garden or in the woods are attracted by this large weed and its fruit and, mistaking it for some edible fruit, eat it in relatively large amounts. Because of the potential danger from this source, a report of two cases of stramonium poisoning together with a review of the subject is thought to be of value.

CASE 1.—H. C., a five-year-old white boy, was admitted to the Children's Hospital on Oct. 24, 1932, because of dilated pupils, thirst, increasing disorientation and motor excitement of five hours' duration.

The child had developed normally and had enjoyed good health until the onset of his presenting illness.

The patient had been playing in the yard with other children during the morning, but his mother noticed that he entered the house several times for drinks of water which he took with avidity. Shortly after the onset of the thirst and six hours before entry, it was noticed that the pupils of his eyes were widely dilated and that his lips were dry and purple. He was given 3 teaspoonfuls of castor oil and was put to bed, where he slept for two hours.

Three hours before admission he awakened from his sleep, was incoherent in his speech, cried out lustily, was unsteady on his feet, and reached for imaginary objects. Jerking movements of the arms and legs were noted. These symptoms increased in intensity, and his family physician recommended hospitalization.

The patient was a well-developed boy of five years with slightly flushed face, tossing wildly about in bed, picking at imaginary objects in the air, and speaking incoherently. The skin was warm and dry, and the throat was dry and red. The pupils were dilated and fixed; the heart rate was 124 per minute.

Atropine poisoning was suspected because of the widely dilated pupils, dry throat, tachycardia, and motor excitement. Soon after entry the patient vomited some orange juice in which was mixed green pulpy material, containing three small reniform seeds each about three millimeters in diameter. The stomach was then lavaged with a 4 per cent solution of soda bicarbonate, but no more seeds were found. The stage of excitement continued for several hours, but gradually he became quiet and spent a restful night. Twelve hours later the child was well oriented and calm, but the pupils continued to be dilated for another twenty-four hours.

The seeds expelled in the vomitus were identified by Dr. Reid Hunt, professor of pharmacology at Harvard Medical School, as stramonium seeds which contain both atropine and scopolamine. It was suggested that the rash, vasodilatation and fever, characteristic of atropine poisoning, were absent because of the inhibiting effect of scopolamine.

Further communication with the parents of the patient revealed the presence of the Jimson weed in their yard. The patient recognized a pod and acknowledged eating the seeds for "peanuts," stating that he cracked open the pods with "a pliers."

The patient made an uneventful recovery, with an afebrile course and was discharged home six days after admission with a diagnosis of stramonium poisoning.

CASE 2.—E. P., a four-and-one-half-year-old white girl, was admitted to the Children's Hospital on Sept. 7, 1933, because of dizziness, delirium, flushed face, and dilated pupils of seven hours' duration.

The child had been outdoors playing with her sisters and some neighbors during the afternoon, and when she was called to supper, it was noted that she was acting queerly. Her playmates said that she was dreaming. She talked incoherently and gave irrelevant answers to questions. When offered water, she spat it back and continued to spit "as if her mouth were full of cotton." Her mother noted that she was flushed and that her eyes were "starey." She was given an enema. Her family physician suspected drug poisoning, and finding no possible causative drug in the house, advised admission to the hospital for observation.

On arrival at the hospital, the child was irrational, making purposeless gyrations with her arms, going through the motions of blowing kisses with her hands, and of plucking things out of the air. Except for flushing of the face with circumoral pallor, dilated fixed pupils, a dry mouth covered with sticky saliva, and a rapid bounding pulse, examination was negative.

The mother was carefully questioned concerning the ingestion of atropine or of the possibility of the child's having eaten any weeds or plants, but any such knowledge was denied.

The admission diagnosis was atropine poisoning, but to rule out a possible early encephalitis, a lumbar puncture was performed, which yielded a normal spinal fluid. Gastric lavage yielded nothing of aid in the diagnosis. She was given 1/30 grain of pilocarpine and 1½ grains of sodium luminal, subcutaneously.

Upon returning home, the mother awakened the other children and on close questioning found that the patient had eaten seeds from a pod which one of the neighbor children had brought into the house. The mother found one of the pods and brought it to the hospital. The pod was recognized by Dr. Hunt as the fruit of the Jimson weed.

In the course of twelve hours the patient became rational, and the pulse rate dropped to normal. The pupils continued to be dilated for twenty hours. At no time was the temperature elevated.

The child made an uneventful recovery and was discharged two days after entry with a diagnosis of stramonium poisoning

The symptoms of stramonium poisoning are variable in their degree and nature because of variations in the amount of the respective alkaloids, atropine, and scopolamine. Depending on the amount of the drug and the form in which it is taken, the onset occurs from ten minutes to four hours after ingestion. In criminal poisoning, in which the powdered drug is taken in food or beverage, the onset of symptoms is very rapid, but in children, in whom the leaves or seeds are taken without being thoroughly chewed, the symptoms are more gradual in their onset.

According to Ismael[8] there are two forms of symptoms: the maniacal form from seed poisoning and the comatose form usually seen when the leaves are the causative agent. Variations between these two forms are not uncommon.

In the maniacal form the patient is boisterous; his speech is impetuous and incoherent; his actions are impulsive and exaggerated; he reaches for imaginary objects and attempts to pull threads from his fingertips. His activity may be of a destructive nature, manifested in attempts to harm himself or those about him. After a variable period of time, usually from twelve to twenty-four hours, the maniacal stage may pass into the comatose form, which is marked by degrees of unconsciousness, varying from mild stupor, from which the patient may be easily aroused, to profound coma, in which the temperature is subnormal, the pulse feeble, and the respirations slow and stertorous, accompanied by a deep cyanosis.

One of the earliest symptoms of poisoning is extreme thirst, and the patient attempts to drink large quantities of water. This may initiate vomiting, which, however, is not a constant finding, due to relaxation of the pyloric sphincter. On the other hand, constipation and urinary retention are quite constant, due to the inhibitory action of the drug on the parasympathetic system. Convulsions of a tetanic nature are de-

scribed by van Ravenswaay[18] in one of his cases, and Ismael[8] describes clonic convulsions with retraction of the neck and opisthotonus simulating meningitis.

Objectively, the pupils are dilated and fixed; the skin is dry and flushed with a diffuse nonpunctate erythematous rash; and the pulse is rapid and weak with a tendency to dicrotism. The temperature is variable, but in several cases, notably those reported by Garvin and Ruh,[3] and van Ravenswaay,[18] a fever as high as 105° F. is recorded. Because of salivary inhibition and vasodilatation, the pharynx and tonsillar fauces may appear intensely red and injected.

Ordinarily, the symptoms subside in twelve to forty-eight hours, and the patient becomes quite normal except for ocular dilatation, which may continue for seven to fourteen days. Characteristically, the patient remembers nothing of his condition during the previous period. Although recovery is usually complete, Lenoir[10] described three cases in which insanity persisted, and a case of permanent amentia is described by Zakarias.[21] When large amounts of atropine are present in the seeds, the symptoms are prolonged and serious. It is the amount of scopolamine that is present which masks the symptoms usually associated with atropine poisoning and which accounts for the lack of fever, rash or evidences of vasodilatation. The effects from this drug are not so serious or lasting.

The treatment of stramonium poisoning is directed toward preventing further absorption of the drug and toward symptomatic relief. The first step is the removal of the poison from the gastrointestinal tract. This may be accomplished by stomach lavage with water. The use of 4 per cent tannic acid solution is recommended by Gimlette,[4] as this precipitates the alkaloids. This author suggests the later use of potassium permanganate solution in 1:5,000 dilution to oxidize any of the remaining drug. In children, in whom gastric lavage is difficult, induction of emesis by apomorphine subcutaneously, or by ipecac orally, is justified. The removal of the drug from the intestines may be hastened by large doses of magnesium sulphate by mouth; in urgent cases, the use of croton oil by mouth or surgical pituitary extract subcutaneously has been recommended.

After the amount of ingested drug has been reduced to a minimum, efforts should be made to induce rest and quiet. The patient should be kept in a quiet, dark room with careful nursing supervision, under restraint, if necessary, to prevent injury. Sedatives such as paraldehyde or the barbiturates may be given. Warm packs are useful in obtaining relaxation, and the diaphoresis so obtained is said to hasten excretion of the drug. In severe cases, a 25 per cent solution of magnesium sulphate given intramuscularly may be helpful, care being taken to avoid excessive fall in blood pressure.

The use of morphine has been suggested to secure rest, but it probably should be given sparingly because of the synergistic action of morphine with atropine and scopolamine.

Pilocarpine, the physiologic antidote, having an antagonistic action on the parasympathetic system, has been used in the treatment of stramonium poisoning, but because of the difficulty in estimating the amount of the offending drug that has been ingested, accurate use is impossible. When used, pilocarpine should be administered in repeated small doses until the desired effect has been obtained. Pilocarpine is contraindicated in elderly people because of its tendency to cause pulmonary edema instead of diaphoresis.

Fortunately the number of fatalities from accidental poisoning with stramonium is small. Variable amounts of the drug have been found in fatal cases, but the lethal dose is difficult to estimate since the toxic symptoms would necessarily be caused by the digested seeds, rather than by those found in the alimentary canal. McNally[11] in 1915 reported the case of a seven-year-old boy who died fourteen hours after the ingestion of the seeds. During this time he had shown the clinical evidences of excitement, followed by coma and dry stertorous respirations. At autopsy, several hundred small petechiae over the epicardium were found. The lungs were distended with hypostatic congestion in both bases, and a few subpleural hemorrhages were noted. One hundred seeds were found in the gastrointestinal tract.

McNally[11] also recorded the death of a child of two and one-half years after the ingestion of sixteen seeds. An Indian laborer died in seven and one-half hours; examination of the stomach contents from the case revealed eighty-nine seeds.

In addition, Hurshberger[7] in 1909 mentioned the death of a three-year-old child, resulting from the ingestion of stramonium seeds. Pammel[14] refers to two cases about metropolitan New York in boys under five years of age. One of these patients was known to have obtained the seeds from a plant in a public park.

According to Lenoir,[10] Gimlette,[4] and Ismael,[8] deaths from criminal poisoning are more common since the powdered drug is used. The dosage is difficult to estimate, and, whereas the amount given is intended only to incapacitate the victim to facilitate robbery, death often results from overdosage. Lenoir described the fatal case of a convict who used the drug as a means of suicide. Falck, as quoted by Kobert[9] in 1906 stated that death occurred in 11.6 per cent of the collected cases of atropine and hyoscyamine poisoning.

SUMMARY

Historical references to the use of stramonium are noted, and the recent literature has been reviewed with respect to the biology and

pharmacology of the drug together with the incidence, symptomatology, and treatment to be followed in cases of poisoning resulting from its ingestion.

Two cases of stramonium poisoning in children, with complete recovery, are reported.

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143 PARK STREET

DENTAL CARIES

A Calcium and Inorganic Phosphorus Blood Serum Determination

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BLOOD serum calcium and inorganic phosphorus determination is a part of our routine examination in patients in whom such findings might be of value. Among those in whom such examinations were made were forty-eight patients with defective teeth.

The Kramer-Tisdall method was used for estimating blood serum calcium and the Benedict-Theis method for estimating inorganic phosphorus.

In this group there were twenty-four males, twenty-four females.

Age of Patients		*Physical Condition*
Under 5 yr.	25	Good in 25
5 to 10 yr.	21	Fair in 21
10 to 15 yr.	2	Poor in 2

If we look upon 9 mg. of calcium in 100 c.c. serum as the low normal for children, forty-six of these patients had normal serum calcium. In a boy thirteen years old the calcium was slightly lowered, 8.936 mg.; a boy ten years old showed 8.964 mg. calcium, both practically normal.

If the normal phosphorus content is considered as from 4 to 6 mg. in 100 c.c. serum, the phosphorus was normal in all. These patients were not children with a filled cavity or two, but they had gross lesions as is evidenced by the fact that they were referred to us by dentists and family physicians for calcium determinations. It is evident that in these children there were present factors for the dental caries other than the calcium and phosphorus content in the blood serum, which serves simply as a transportation medium between the gut and the osseous system and from there to the kidney and gut for excretion.

The vast amount of literature accumulated during the past few years as to the etiologic factors in dental caries in children is characterized by the positive opinion and frank disagreement of the various authors. Our clinical observations of many hundreds of children in whom appraisal of the dental condition has been included in the examination lead us to believe that nutritional agencies, dental hygiene, bodily disorders, both acute and chronic—play a rôle, important but secondary to a fundamental constitutional error as a cause of dental caries. Again from the clinical point of view, two diseases of children show pronounced dental defects as a part of their symptom-complex. The tooth condition is an outstanding feature of the stigma and is in itself diagnostic in those conditions. We refer to syphilis (congenital) and hypothyroidism (cretinism). These are two constitutional disorders in children in which

the teeth rarely escape involvement and in each disease show characteristic pathologic manifestations. All are familiar with the bony changes in congenital syphilis. Osteochondritis and dactylitis are observed as early as the third month of life in many instances, and time and again Hutchinson's teeth have been the only suggestion of congenital syphilis in a patient during an examination, and corroboration of the diagnosis of syphilis being proved by a four-plus Wassermann reaction.

In the cretin the teeth usually show delay in eruption and invariably a gross pathology at later periods. Engelbach[1] writes as follows: "Among forty-three cases of juvenile thyropituitarism eighteen showed orthodontic changes such as overcrowding, malposition, defective calcification with decay of the teeth."

The family history of dental caries carries with it the suggestion of a constitutional ailment. In the vast majority of parents of children with carious teeth, inquiry and examination showed the child was carrying on the familial defect. When a group of children show a profound selective pathologic tooth condition of a known etiology, as in the case of syphilis and hypothyroidism, it is logical to assume that a lesser manifestation of the stigma might be a sensitive index, perhaps the remotest indication of the disability and without other signs of physical derangement. In this connection it is fair to assume that caries in the young may be due in part to a systemic deficiency with failure to produce and maintain a tooth structure capable of resisting the various agencies that may prove destructive.

It is our belief that dental caries may be prevented in many children through recognition of defects in the parents and the introduction of replacement measures at the onset of pregnancy. When the thyroid gland is better understood, it will be found that it possesses possibilities of varying functional capacity under varying conditions of bodily vigor. We have demonstrated in our study, "Fatigue in School Children,"[2] incident to social demands, school activities, and adolescence, that there may be a temporary inability of the thyroid gland to meet the demands placed upon it, as demonstrated by means of the basal metabolism test, the blood pressure, and functional cardiac manifestations. This observation was further corroborated therapeutically through the administration of the desiccated thyroid gland. It is not beyond the bounds of reasonable conjecture that gravidity with its demands upon the female might call for a greater thyroid hormone supply than the individual can furnish with the resulting characteristic remote effects upon the child, both antenatal and postnatal.

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132 WEST EIGHTY-FIRST STREET

ENCEPHALITIS AND MYOCARDITIS IN A FATAL CASE OF TRICHINOSIS

Report of a Case in a Fourteen-Year-Old Girl

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THE present case of trichinosis is reported because of several interesting points: (1) the predominance of a picture of encephalitis throughout the entire course; (2) the absence of three generally accepted diagnostic criteria, gastrointestinal symptoms, muscular tenderness, and eosinophilia until the day preceding death; (3) death of the fourteen-year-old girl; and (4) changes in the brain and myocardium found on postmortem examination.

Six individuals, five adults and one girl, fourteen years old, had eaten pork sausages on Jan. 21, 1934. Within a few hours to a few days the members of the group complained of symptoms which were considered as influenza as manifested by general muscular pains, fever, headache, abdominal pains, and weakness. Four of the group made uneventful recoveries at home. The girl, who was admitted to a hospital, is the subject of this report. The brother was admitted to the Israel Zion Hospital on the day preceding her death. He ultimately recovered but presented a picture of transitory encephalitis for two days after admission. Trichinae were found in his deltoid muscle on biopsy.

We have been able to obtain a record of the eosinophile count and of later blood counts in some of the group.

The meat had been obtained from the same butcher with whom the family had been dealing for many years, and it bore the stamp of inspection of the United States government. The sausages were prepared from the pork, dried and suspended, by the family. We understand that they were then fried before being eaten.

CASE REPORT

H. M., fourteen years old, became ill with what was considered to be the grip, manifested by high temperature, sore throat, joint pains, and general soreness. The condition became aggravated; the fever continued, and eight days after the onset edema of the eyes appeared. She was admitted to the Israel Zion Hospital on the twelfth day of her illness. For the previous two days she had been in another hospital where her condition had been diagnosed as influenza complicated by acute nephritis.

From the Departments of Pediatrics and Laboratories, Israel Zion Hospital.

On admission she presented the following clinical picture: Patient was a fairly well-developed Italian girl who was toxic, apathetic, drowsy, and delirious at times. Both eyes were inflamed and showed edema of the upper and lower eyelids. The throat was congested and dry with sordes on lips and teeth. There was a slight cervical adenitis. The ears were negative. The lungs and abdomen did not present any abnormal findings. A roughened systolic murmur was localized at the apex; the myocardial sounds were of fair muscular quality and regular in rhythm. No eruptions or petechiae were noted on the skin or mucous membranes. There were no signs of meningeal irritation.

Since a slight nuchal rigidity and bilateral Kernig sign were noted the next day, a lumbar puncture was made. Impaired resonance and diminished breathing were noted over the left posterior part of the chest. The blood pressure was 100 systolic and 70 diastolic. The edema of the face had subsided.

On the following day the picture was more that of encephalitis with continued drowsiness, ptosis of the left eye, and delirium. Dullness and distant breath sounds were noted at both bases. Examination of both fundi revealed slightly congested vessels without any alteration in the discs. The temperature ranged from 103° to 106° F. with a terminal point of 108°; the pulse varied from 130 to 170, was regular and of fair tension and volume; the respirations were between 45 and 58 per minute. We were never able to elicit any muscular tenderness in her lucid moments. Death occurred on the nineteenth day after the onset of her illness, or the seventh day after admission to the hospital. The treatment consisted of general supportive measures, hypodermoclyses of 5 per cent glucose, blood transfusion, and sedatives when indicated.

The blood count on admission revealed leucocytosis but no eosinophiles, a second count showed only 3 per cent eosinophiles, and a third, taken the day preceding death, showed an increase to 12 per cent eosinophiles (Table I). The blood serology showed

TABLE I

BLOOD EXAMINATIONS

DATE	R.B.C.	W.B.C.	HG. %	POLY. %	LYMPH. %	MONO. %	EOSIN. %	BASO. %
H. M. (Died Feb. 19, 1934)								
2/ 3/34	4,180,000	20,000	80	91	7	2	0	0
2/ 6/34	3,900,000	10,500	80	85	11	1	3	0
2/18/34			80	80	7	1	12	0
A. M. (Brother—recovered)								
2/ 8/34	4,600,000	21,500	80	94	6	0	0	0
2/10/34	4,000,000	18,900		42	9	3	46	0
2/12/34		18,000		43	17	1	38	1
2/14/34		14,000		46	8	3	42	1
2/17/34		7,300		43	16	5	36	0
2/23/34	3,750,000	7,600	75	53	30	3	13	1
8/11/34	4,300,000	5,200		44	54	4	1	0
J. M. (Father—recovered)								
2/11/34							18	
8/11/34	4,500,000	10,000		65	14	1	9	1
J. A. (Cousin—recovered)								
2/11/34							18	
8/11/34	4,500,000	5,300		43	47	7	2	1

a plus or minus Wassermann reaction but a four-plus Rosenthal.[27] Blood cultures were sterile on two occasions. Blood chemistry findings were: glucose, 103 mg.; urea nitrogen, 12.7 mg.; creatinine, 1.42 mg. per 100 c.c. The spinal fluid was clear; 20 c.c. were removed under normal pressure and on examination showed 30 cells to the field, 95 per cent lymphocytes and 5 per cent polymorphonuclears. Albumin was one-plus; globulin, negative; and sugar, reduced. Urinalyses were essentially negative except for a faint trace of albumin.

Search for trichinae in the blood, urine, spinal fluid, and feces resulted in negative findings.

The autopsy was performed by Dr. R. Cares.

Anatomic Diagnosis.—Trichiniasis of skeletal muscles. Acute trichinous myocarditis. Cerebral congestion and edema. Toxic encephalosis. Acute hemorrhagic duodenitis. Focal catarrhal ileitis. Hypostatic congestion of lungs. Cloudy swelling of liver, kidneys, and heart. Subacute infectious swelling of spleen.

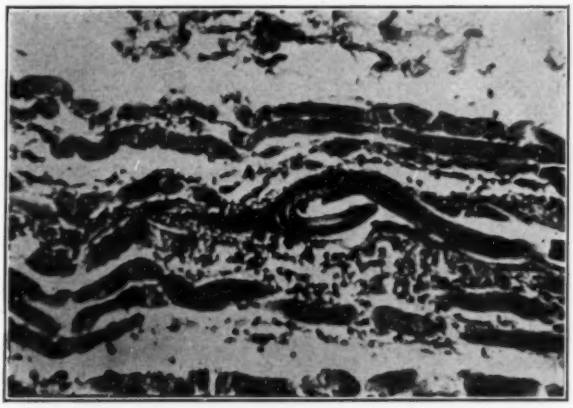

Fig. 1.—Trichinella larvae in diaphragm with marked peripheral cellular reaction (×90).

The essential findings were as follows:

Brain: The dura was tense and slightly congested. When the dura was reflected, the surface of the brain was seen to be slightly edematous; the large veins were congested; there was a distinct increase in the finer arterial subarachnoid ramification over the gyri. The brain was of normal firmness. Multiple section of the cerebrum and cerebellum disclosed a distinct hyperemia of the gray matter, which assumed a pink appearance throughout. The white matter presented only punctate hyperemia of the severed small vessels. The spinal fluid was slightly increased in amount but was clear.

Heart: The pericardium contained 1 ounce of clear fluid. The right ventricle was thin walled and somewhat flabby; the left ventricle was contracted. The myocardium was 1.5 cm. thick, of a dull, brownish red color. All valve cusps were thin and smooth.

Gastrointestinal Tract: The duodenum contained a copious amount of distinctly bloody gelatinous secretion. (Examination of duodenal contents disclosed no evidence of trichinae or other parasites.) The mucosa was hyperemic. This hyperemia extended into the proximal two feet of jejunum and was most marked at the apices

of the mucosal folds. The rest of the small intestine was slightly dilated. Dark blue hemorrhagic areas 0.5 cm. in diameter were scattered throughout the serosa. There was a dirty grayish green fibrinous exudate near the terminal ileum with some congestion of the serosa.

Microscopic Findings.—(Stained with hematoxylin eosin.) Brain: Sections from parietal lobe showed that the pial membrane was slightly thickened with a sparse

Fig. 2.—Trichinous myocarditis with focal cellular infiltration (×100).

Fig. 3.—High power magnification of field shown in Fig. 2. Focal destruction of muscle fibers with mononuclear collection. One large macrophage is seen (×450).

infiltration of mononuclears and an occasional macrophage. Infrequently the cortical cells revealed slight nuclear chromatolysis. The Virchow-Robin spaces were slightly widened. The glia cells were slightly increased in number; this was most noticeable in the vicinity of the capillaries. All cortical capillaries were immensely engorged and prominent throughout. Some interstitial edema was present in all sections.

Heart: Distinct interstitial infiltrations, focal in character, were noted throughout; a number were perivascular in location. The majority of the cells were

histiocytes with numerous mononuclears and an occasional neutrophile. The adjacent muscle fibers were disrupted and frequently disintegrated. A number of the cellular foci showed red cell extravasation. The muscle fiber striations as a rule were well preserved. Careful study of numerous serial sections from several blocks failed to disclose the presence of trichina larvae.

Skeletal Muscle: The muscle fibers throughout the diaphragm were the seat of cloudy swelling and occasional hydropic degeneration, with numerous areas showing coagulation necrosis. There was a rather widespread interstitial cellular infiltration in focal collections for the most part. The cells consisted of approximately equal proportions of neutrophiles; mononuclears with abundant, sometimes ameboid, basophilic cytoplasm; and macrophages containing engulfed red cells with degenerating nuclear remnants or vacuoles.

In the center of a number of these cell clusters were noted sections of the trichina larvae; the adjacent muscle fibers were in various stages of degeneration. The larvae were surrounded by a pseudolining of flattened mononuclear cells enclosing a slightly granular, pink-staining substance. Not infrequently multinucleated giant cells were located at one pole of the encapsulated lesions. Appreciable fibroblastic proliferation was not seen. Additional sections from the psoas and abdominal muscles revealed essentially the same inflammatory myositis, with distinctly less cellular infiltrations and only an infrequently encountered trichina larva.

COMMENT

Case reports of trichinosis in children are fairly frequent in the literature. In the series of van Cott and Lintz,[1] four of the ten affected were children as were eight of the eleven in the report of Reifenstein and his coworkers.[2] One of the patients in the former series nursed her infant throughout the entire course until she was incapacitated, but the infant remained well. The authors considered this as evidence that trichinae are not transmitted through maternal milk and that a nursing mother does not infect her nursling. On the other hand, Salzer[3] reported the finding of trichinae in mother's milk and in excised mammary tissue.

There is a general tendency to consider the disease a mild one in children, both as to morbidity and mortality. The death rate in children is less than the average of 5.6 for all ages. The mildness of the disease in children is due to the probability that they eat less meat and thereby ingest fewer trichinae. McCoy[4] noted experimentally a mathematical relationship between the amount of ingested meat and the severity of the disease. Other factors are considered by some to be responsible for the mild course in children: 1. Weakness of the gastric juices which interferes with liberation of the encapsulated trichinae. 2. Expulsion of large amounts of undigested particles of infected meat in the frequent bowel movements. 3. Shortness of the gastrointestinal tract. These reasons are probably more speculative than conclusive.

The symptoms may be divided into three stages which are more or less defined and manifest clinically the life history of the parasite. The stage of intestinal infestation may occur in a few hours or several

days after the ingestion of the meat. This is followed by the stage of dissemination in which the embryos invade the lymphatics and blood stream and attack the muscles. Trichinae have been found in spinal fluid, blood, feces, maternal milk, mammary tissue, and in other regions. The stage of regression or encystment of the larvae begins at about the end of the fourth or fifth week.

The manifestations are continued fever, muscle pains, especially of the gastrocnemius and biceps, abdominal pains, and diarrhea. Pepper[5] stated that diarrhea is more marked in children and may be a probable explanation of the mildness of the cases in this age group. It is interesting to note that in our fatal case there was an absence of diarrhea and severe gastrointestinal symptoms. Marked edema of the face, especially about the eyelids, is a prominent symptom, and is considered by some to be due to occlusion of the local capillaries by the embryos. The picture may simulate muscular rheumatism, typhoid fever, gastroenteritis, encephalitis, and meningitis.

A number of observers have noted the preponderance of meningitic and encephalitic symptoms. Meyer[6] reported three instances in children in whom diagnoses of cerebrospinal meningitis had been made upon the strength of neck rigidity, positive Kernig sign, absent knee jerks, delirium, irritability, and photophobia. The spinal fluids were all clear and showed on cytologic examination from 40 to 240 cells to the cubic centimeter. Trichinae were found in one case. Pund and Mosteller's[7] patient was an eleven-year-old girl in whom symptoms of encephalitis occurred three weeks after vaccination against smallpox. Walker[8] noted a meningitic picture in a boy after the ingestion of bear meat which was later found to be loaded with trichinae. Van Cott and Lintz were the first to obtain the trichinae from the spinal fluid of a patient who presented symptoms and signs of acute meningitis.

Pund and Mosteller reported four instances in the literature, in addition to their own case, in which trichinae were present in brain tissue. Bloch and Hassin[9] reported microscopic findings in the brain, which consisted of rather sparse lymphocytic infiltration, perivascular vacuolization, and marked capillary congestion. We were able to note a similar diffuse degenerative action, obviously nonspecific. We are in accord with the viewpoint of Gruber and Gamper[10] that central nervous system changes in trichinosis are analogous in nonspecificity to those found in the brains in cases of malaria, typhoid fever, and other systemic infections.

The number of larvae in the brain, even after scrutinizing search, does not approximate that found with greater ease in striated muscles. Cellular inflammatory response in nervous tissue as manifested by leucocytic and glia cell collections or focal hemorrhages is undoubtedly due to the transient presence of parasites in the brain.

There is a discrepancy between the clinical picture of encephalitis and the paucity of severe organic changes in the brain in Case 1. We cannot estimate to what extent the mild microscopic inflammatory changes are responsible for the symptomatology. The slight meningeal reaction noted both clinically and histologically does not compare with the definite clinical pictures observed by Gruber and Gramper,[10] Knorr,[11] and Chasanow.[12] It is interesting to note that even these observers failed to find a definite relationship between the degree of tissue destruction and the severity of the clinical reaction.

Larvae of trichinosis were first demonstrated in heart muscle by Zenker[13] in 1860. Though we were unable to find any even after diligent search in several hundred serial sections, we observed a rather widespread focal myocarditis. Several investigators state that the cellular myocardial reaction is due to the previous presence of the larvae during the invasive stage. Degenerative and exudative myocarditis have been noted by several observers.[7, 10, 14, 15] Zoller[16] and Dunlap and Weller[17] observed the larvae of trichinosis in the heart muscle of experimental animals as early as the fifth day after infestation. The irritative cellular response evoked by their presence outlasted their emigration for permanent quarters in skeletal muscle a few days later. No larvae could be found in the animal's heart muscle after the second week.

Eosinophilia as a diagnostic criterion has been stressed by Brown,[18] Adami,[19] Chasanow[12] and by others to such an extent that it has assumed a sine-qua-non position in the diagnosis of trichinosis. Brown's original case showed an eosinophilia of 68.2 per cent; Reifenstein and his associates[2] found an average of 24.5 per cent in their series. Others feel that eosinophilia is not a constant or invariably dependable finding nor is the degree of eosinophilia a criterion of the severity of the disease. It may be absent throughout the entire course or may not appear until the convalescent stage. Reifenstein and his associates, on the basis of an extensive review of the literature, stated that cases which fail to exhibit eosinophilia throughout the entire acute stage are to be regarded as those in which recovery is unlikely. Pepper and others have also noted the absence of eosinophilia in severe and fatal cases. These observations are confirmed to a great extent by the findings in our case which did not show any eosinophilia until twenty-four hours before death. Marked eosinophilia was present in the blood of the other three patients in our group in the acute stage. It is interesting to note that in the brother no eosinophiles were found in the admission examination. The eosinophilia subsided with the acute stage in two of the three patients and was still present in one (the father) six months later.

New diagnostic approaches in trichinosis have been indicated by Bachman[20] who recently has described a precipitin reaction and an

intradermal test. The few experimental and clinical studies which have been reported[21, 22, 23] are inconclusive as to their values. The consensus of opinion seems to be that the skin test is of more practical application but that it is of limited aid in the first few weeks of the illness.

Any measures which will aid in earlier diagnosis will make possible more efficient treatment. The latter should have for its object the expulsion of the trichinellae and the killing of the young larvae before they get into the blood stream. The most opportune time would be in the gastrointestinal stage and may be accomplished by catharsis and an helminthic like hexylresorcinol or thymol.

In the hands of Salzer[3] human convalescent serum gave beneficial results. Almost complete prophylaxis was obtained in animals which had previously been fed infected meat. Beneficial results were also obtained in human subjects as indicated by the temperature, eosinophilia, and general course of the disease. The injection of nonimmune serum and salvarsanized serum did not give the same results. Nieto,[24] however, reports prompt recovery after three intravenous injections of neosalvarsan (0.015 gm. for every kilogram of body weight). Schwartz and Alexander[25] did not succeed in obtaining any of the beneficial results with convalescent serum reported by Salzer.

Riley and Scheifley[26] suggested the extension to small plants of the federal regulations regarding the preparation of sausage and other pork products which are ordinarily consumed without being cooked. They also call attention to the fallacy that government-inspected pork is free from trichinae. Microscopic examination for trichinae was discontinued by the government in 1907, and there is no attempt to carry out any such examinations at the present time in any part of the United States. The best form of prophylaxis is adequate cooking of pork products prior to consumption. It would be best to eliminate all pork products from the dietary of children.

SUMMARY

A fatal case of trichinosis is reported in a fourteen-year-old girl who presented a predominating picture of encephalitis throughout the entire course. Three generally accepted diagnostic criteria of the disease were absent: gastrointestinal symptoms, muscular tenderness, and eosinophilia (until the day preceding death). On postmortem examination myocarditis, cerebral congestion and edema, and toxic encephalosis were found. Studies of the diaphragm, psoas, and rectus abdominalis disclosed heavy infestation by the parasites in the early stages. The brain findings were scant in proportion to the pronounced clinical picture of encephalitis. Blood studies in five individuals affected at the same time are presented. Trichiniasis of the right deltoid was found in a brother who presented a transitory encephalitic picture and recovered.

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A CLINICAL AND CHEMICAL STUDY OF NONDIABETIC KETOSIS WITH ACIDOSIS

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ALTHOUGH many studies[1] of ketonuria in nondiabetic children have been reported, no studies reveal the effect of nondiabetic ketosis on the serum electrolytes. This paper reports electrolyte studies on twenty patients with nondiabetic ketosis. Since the study includes only such patients presenting symptoms suggesting acidosis, only three failed to reveal appreciable reduction of serum bicarbonate. The latter are included since they probably exhibit the typical chemical changes in the blood produced by mild ketosis demanding but little special treatment. The other patients probably represent the types of cases with acidosis associated with nondiabetic ketosis which enter the pediatric wards of a hospital.

Methods.—The electrolyte determinations were all carried out on venous serum by the following methods:[2] bicarbonate, Van Slyke and Neill; chloride, Van Slyke; protein, macro-Kjeldahl; total base, Stadie and Ross; sodium, Barber and Kolthoff; phosphorus, Benedict and Theis;[3] and potassium, Hald's modification of the method of Shohl and Bennett.[4] Blood sugar was determined on a Somogyi[2] precipitate by the method of Shaffer and Hartmann.[2] A slight modification of the method of Scott-Wilson[5] was used to determine acetone. One cubic centimeter of concentrated sulphuric acid was added to a protein-free filtrate of either whole blood or serum and the acetone distilled into Scott-Wilson reagent. The mercurial precipitate was separated by centrifugalization and washing with water and centrifuging again. The precipitate was then dissolved in a mixture of HNO_3 and H_2SO_4, oxidized by heating and titrated with N/20 NH_4SCN, using solid ferric ammonium chloride as an indicator. The method is only approximate with the quantities used (equivalent to ½ to 1 c.c. of blood), the error being about 20 per cent. The results are reported as quantitative since in most cases the approximate result was all that was needed for understanding the acid-base balance, and more accurate results would have required more blood than would have been available if the other studies were carried out simultaneously.

CLINICAL ASPECTS OF THE CASES OF NONDIABETIC KETOSIS

Since previous studies have been carried out largely on cases of so-called "recurrent vomiting," it is desirable to present a short analysis of the material from a clinical point of view. Brief case histories are given in the appendix, but the chief points to be emphasized are summarized in Table I.

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TABLE I

CLINICAL ASPECTS OF CASES OF KETOSIS

CASE	SEX	INFECTION	AGE (YR.)	OUTCOME	W.B.C. THOUSANDS PER C.MM.	TEMPERATURE (C.)	LIVER SIZE	ACIDOSIS
		Cases With Minimal Infection						
1	M	Recurrent vomiting (A)	1.2	R	33	37.8	++	++
1	M	Recurrent vomiting (B)	1.2	R	6	37.5	++	++
2	F	Recurrent vomiting	3.5	R	12	37.5	0	+
3	M	Recurrent vomiting	4.0	R	10	37.5	+	0
4	M	Isolated attack of ketosis	1.2	R	9	38.0	++	++
5	M	Isolated attack of ketosis	5.5	R	5	38.0	0	+
6	M	Methyl salicylate poisoning	2.0	R	10	37.5	±	+
7	F	Newborn, encephalopathy		R	18	37.5	+	++
		Cases With Moderate Infection						
8	M	Alimentary anemia, pharyngitis	2.0	R	32	40.0	++	+
9	M	Congenital heart disease	8.0	R	9	38.0	++	+
10	M	Isolated attack of ketosis	2.5	R	10	38.0	0	+
11	M	Bronchitis	4.0	R	15	37.5	0	0
12	F	Bronchitis	5.0	R	11	39.0	0	0
13	M	Bronchiolitis	5.0	R	17	39.0	0	0
		Cases With Severe Infection						
14	F	Pneumonia	2.5	R	45	40.0	±	+
15	M	Scarlet fever, mastoiditis	2.5	R	19	38.5	++	++
16	M	Scarlet fever, septicemia	4.0	R	15	40.0	++	+
17	M	Enterococcal septicemia, peritonitis	1.0	D	18	40.0	++	++
18	F	Bronchiolitis, bronchopneumonia	0.9	R	19	40.0	++	++
19	F	Sepsis neonatorum (*Str. hem.*)		D	?	37.8	++	++
20	M	Undiagnosed	0.8	D	25	37.5	++	++

Seven cases showed few or no evidences of infection. Although the same patients might be considered to suffer from moderate infections by some physicians, observation of the course in the hospital never revealed serious infections, and such evidences of infection as were found on admission may be interpreted otherwise. Since a red pharynx is characteristic of practically all patients suffering from acidosis and dehydration, particularly when vomiting occurs, this finding was disregarded unless it persisted after the acidosis was relieved. Similarly, leucocytosis and slight transient fever were regarded as manifestations of dehydration in patients who otherwise showed no manifestation of infections.

The cases with minimal evidences of infection included three cases of "recurrent vomiting" and two cases with isolated attacks of vomiting and ketosis which seemed similar to the attacks which recurred.

Case 10 probably also belongs in this group, but evidences of infection were so definite that it was placed in the group suffering from moderate infection.

Attention is called to Case 6 (methyl salicylate poisoning) since it represents the only case in which no vomiting occurred. The patient was lavaged in the hospital about three-quarters of an hour after swallowing about one-half ounce of oil of wintergreen. Since ketosis has been reported in poisoning with methyl salicylate,[6] the child was kept in the hospital despite the fact that he appeared well. He was given 500 c.c. of physiologic saline solution subcutaneously and 200 c.c. of 10 per cent glucose intravenously. Despite this treatment, clinical and chemical evidence of mild ketosis with acidosis was found eighteen hours later.

In Case 7 a severe ketosis developed in a newborn infant following vomiting, inability to take water and food by mouth, and severe dehydration. At six months of age the patient was spastic, microcephalic, and markedly deficient in mental development. The cause of the defective development of the brain might conceivably have been a cerebral injury at birth, but the symmetrical nature of the lesions indicated that a developmental defect or cerebral degeneration was more likely. The case brings out the fact that severe ketosis can occur in newborn babies (see also Case 19).

The six cases with moderate infection are of little interest since they showed but mild ketosis and acidosis. Since in these patients vomiting was quite severe in all but one (Case 9), they illustrate that marked vomiting alone does not produce severe ketosis. In Cases 9 and 10 the patients suffered from mild upper respiratory infections.

The seven cases with severe infection are of especial interest since they show the importance of recognizing that ketosis can play a prominent rôle in some infections. While the infections probably played the chief rôle in the illnesses, successful treatment of the ketosis and acidosis undoubtedly was responsible in large measure for the favorable outcome in certain cases (Cases 15, 16, and 18). Although three cases were associated with infections due to hemolytic streptococci (Cases 15 and 16, scarlet fever; and Case 19, sepsis neonatorum), such factors as vomiting and age seemed to play the chief rôle in the development of ketosis rather than the type of invading organism. In Case 16, it was striking that ketosis persisted as long as the liver remained large, despite administration of intravenous glucose.

The effects of ketosis did not apparently lead to the fatal outcome in Cases 17, 19, and 20. In Case 17, the patient suffered from enterococcal peritonitis and sepsis, and in Case 19, from streptococcal sepsis and encephalitis. Although the cause of death was not determined in Case 20, chemical and clinical evidences of ketosis, acidosis, and dehydration were absent at the time of death. However, the patient re-

mained in coma and shock and a terminal rise in temperature to 40° C. occurred. The clinical course suggested encephalitis although the negative blood cultures do not entirely exclude an overwhelming bacterial infection.

The ages of the patients are of especial interest. Two were newborn infants who suffered from cerebral disorders. Four were under one year of age, and ten under two. Of the nine admissions during which the serum bicarbonate was found to be below 11 milliequivalents per liter (26 volumes per cent), seven were younger than fifteen months, and the other two were aged two and one-half and four years, respectively. *Ketosis with acidosis apparently is more frequent and severe in infants younger than a year and a half.*

Of the nineteen patients, only five were girls. While the series is small, the preponderance of males may represent a significant difference rather than a chance selection of cases. The literature reveals about an equal distribution between boys and girls in recurrent cases.

Fever was absent or slight except in the presence of infection. Leucocytosis over ten thousand unrelated to obvious infections occurred only three times. In Case 1 A and Case 7, the leucocytosis was presumably related to severe dehydration. Since comparatively mild infections often lead to marked leucocytosis in cases of alimentary anemia, the high count in Case 8 was probably associated with the infection and anemia rather than with the ketosis, acidosis, and dehydration.

Enlargement of the liver* was striking in this series of patients. Only Cases 2, 5, 6, and 10 failed to show enlargement of the liver in the presence of well-developed ketosis. In Cases 11, 12, and 13, the liver was not enlarged, but these patients can hardly be considered examples of severe ketosis. The enlargement of the liver was apparently not related to cardiac failure except perhaps in the patient with a congenital lesion of the heart (Case 9). Although circulatory failure was undoubtedly present in the patients who were markedly dehydrated, it does not seem likely that the circulatory failure accompanying dehydration leads to enlargement of the liver since a similar grade of dehydration in diarrhea is not accompanied by enlargement of the liver. None of the patients was jaundiced, and, while the icteric index was not determined, abnormal pigmentation of the serum was not observed when making chemical analyses of the serum. The bloods from two patients with catarrhal jaundice failed to reveal significant ketosis.

ACID-BASE BALANCE OF THE SERUM

Table II gives the results of the analyses of blood.

*In estimating enlargement of the liver, due consideration was given to variations in the relative position of the liver in normal infants and children of various ages. In all patients thought to have enlarged livers, the size decreased during convalescence. In Case 19, the enlargement was demonstrated at autopsy.

TABLE II

CONCENTRATION OF SERUM ELECTROLYTE, BLOOD SUGAR AND N. P. N.

CASE	DATE	'HCO$_3$ M.EQ. PER L.	'CL. M.EQ. PER L.	PROTEIN M.EQ. PER L.	"HPO$_4$ 'H$_2$PO$_4$ M.EQ. PER L.	'ACETONE M.EQ. PER L.	NA+ M.EQ. PER L.	K+ M.EQ. PER L.	T.B.+ M.EQ. PER L.	SUGAR MG. PER CENT	N. P. N. MG. PER CENT	PROTEIN GM. PER CENT
1 A	10/27/29	5.9	117.4	20.0	2.5	8.0			160.0		36	8.09
1 A	10/28/29	19.7	123.4	15.7	1.8	8.0			178.9		30	6.40
1 A	10/30/29	36.8	101.4	12.8					154.6		20	5.17
1 A	11/ 1/29	31.8	102.8	15.3	1.4				157.0	97†		6.20
1 A	11/ 6/29									81†		
1 B	11/16/29*	6.35	106.4	16.3		10.8			156.4	97†		6.58
1 B	11/17/29	14.1	113.4	15.1		2.4			150.9			6.09
1 B	11/20/29	26.9	100.8	16.8					151.0			6.81
2	2/22/33*	13.8	99.7	17.3	2.8	+			138.3	52†		7.2
3	10/31/29*	23.5	107.5	16.8	1.6	2.0				97†	44	6.6
3	11/ 5/29									109		
4	9/14/30*	6.34	103.0	16.5		11.5			146.8	62†		6.66
4	9/15/30	12.1	104.2	14.8	2.7	4.1			149.2	185		5.83
4	9/17/30	19.0	99.6	14.4		3.4			149.4	116		5.82
4	9/23/30					0.9				107†		
5	8/ 3/34*	15.7	99.0	18.6		5.9			147.0	48†		7.51
6	8/26/32	13.01	108.4	15.7	3.6	4.8			142.6		31	6.48
7	12/23/31	7.1	121.3	15.8		14.9			152.0	143	35	6.40
7	12/24/31	15.4	116.0	14.2		2.8			152.0	86†		5.75
7	12/28/31	22.5	103.8	12.5					151.6		43	5.05
8	7/31/32*	15.5	100.7	15.6		4.7			147.0	67†		6.44
8	8/ 1/32	19.6	99.3	16.3		2.3			147.2	105†		6.80

TABLE II—CONT'D

CASE	DATE	'HCO$_3$ M.EQ. PER L.	'CL. M.EQ. PER L.	PROTEIN M.EQ. PER L.	"HPO$_4$ 'H$_2$PO$_4$ M.EQ. PER L.	'ACETONE M.EQ. PER L.	NA+ M.EQ. PER L.	K+ M.EQ. PER L.	T.B.+ M.EQ. PER L.	SUGAR MG. PER CENT	N. P. N. MG. PER CENT	PROTEIN GM. PER CENT
9	1/10/32*	14.8	100.0			10.6				87†		
9	1/13/32	26.8	99.5						144.4			6.25
10	3/10/30*	12.0	109.0	17.1		8.0			155.0	65†		6.85
10	3/11/30	16.9	108.2	15.9		2.8			146.8	108†		6.44
11	5/19/30	19.3	103.0	14.4					139.8		27	6.01
12	4/22/30*	19.9	101.6	15.8	1.9	1.9			146.6	58†		6.38
13	3/15/32*	17.7	102.3	20.4	2.0	5.0	131.8	3.0		89†		8.24
14	6/ 9/34*	15.6	90.0	18.0		2.0	129.0					7.4
15	4/ 8/32	11.3	85.9	21.6		7.8	137.5	2.6		176†	34	8.7
15	4/10/32									139†		
15	4/12/32									65†		
16	3/ 5/30	10.8	101.2	12.2		6.1			130.8	110	55	4.72
16	3/ 7/30	15.1	99.2	13.6		5.5			134.8	99†	28	5.70
16	3/11/30	29.7	101.2	11.9		0.0			162.6	87†	19	5.09
17	2/15/30*	10.1	104.4	12.7	4.4	3.7			149.0		120	5.21
18	12/ 7/32*	5.1	123.2	18.9	3.2	4.5			149.0	102†	60	7.64
18	12/ 8/32	10.8	115.8	14.3		4.4	157.6	3.1		400	32	5.74
18	12/ 9/32	19.1	105.1	13.4		3.0	138.2	3.1		163		5.40
19	1/19/33	7.7	109.1	16.5		7.0			150.3			6.68
19	1/21/33		117.6	10.9		5.6			158.4			4.42
20	10/ 4/30*	5.4	106.0	16.8		4.2			153.4	200		6.81
20	10/ 6/30	21.0	98.8	14.0	2.4	0.9			147.4	132	24	5.60

*Bloods taken without treatment, such as hypodermoclyses, which might alter the concentration of serum chloride and bicarbonate.
†Bloods taken at least six hours after feeding or infusion of glucose.

While blood sugar was not determined on admission in all cases, a sufficient number was obtained to demonstrate that the concentration of blood sugar in cases of severe nondiabetic ketosis seldom differs significantly from that of other hospital patients. In Cases 2, 4, 5, 8, 10, and 11 the values are somewhat low, but not below that found frequently in fasting children. In Case 15, the blood sugar content was so high that diabetes was suspected even though the patient did not strongly suggest the diagnosis clinically. Subsequent determination of the sugar tolerance to intravenous glucose revealed a normal reaction.

The reduction in serum bicarbonate was as great in these patients as one is accustomed to meet in diabetic coma. As pointed out previously, the marked reduction in bicarbonate occurs chiefly in the patients aged less than fifteen months. In most cases the diminution of bicarbonate is only partially explained by accumulation of ketone acids. Increase in chloride was considered in Cases 1 A, 7, and 18. In Case 1 A, the high chloride (117.4 m.eq. per liter) is only partly explained by the hypodermoclysis of 400 c.c. of physiologic saline about eighteen hours before the blood examination. In Case 7 (121.3 m.eq. per liter), a hypodermoclysis of 250 c.c. of saline was given about twelve hours previously. Since intravenous infusions of glucose were given in all cases, the elevation of chloride is probably not explained by the hypodermoclyses. In Case 18 no saline was given before the blood analysis, but the high chloride (123 m.eq. per liter) may be explained by the diarrhea. In Case 15, the chloride was low (85.9 m.eq. per liter).

The concentration of total base was normal in most of the cases, but tended to be reduced in the patients with severe infections. In Case 16, the reduction in total base was considerable (130 m.eq. per liter).

In many of the cases the concentration of acetone was only moderately elevated, but high values were found in Cases 1 A, 1 B, 4, 5, 6, 7, 9, 10, 15, 16, and 19.

The high nonprotein nitrogen in Cases 16 and 18 is probably referable to dehydration and oliguria.

Considerable concentration of the blood was indicated by the initial concentration of serum protein and its subsequent fall in Cases 1 A, 1 B, 4, 7, 18, 19, and 20. A gain in weight during recovery indicated that the loss of fluid was not confined to the plasma. However, the gains in weight, except in cases 1 A, 1 B, 7, 15, 18, and 20, were not as great as one is accustomed to find in alimentary intoxication.

In summary, the chemical findings of the blood reveal dehydration and reduction of bicarbonate due to accumulation of ketone bodies and in some cases to increased concentration of chloride. If one considers the loss of body fluid indicated by the loss in weight and the diminished

skin turgor, the patients must be deemed to suffer from deficit of sodium, chloride, and water in about the proportion they occur in the blood plasma. The blood sugar gives no direct evidence of the nature of the disturbance in carbohydrate metabolism except that it is not like that of diabetes mellitus.

RESULTS OF TREATMENT

The general plan of treatment of these patients was as follows: (1) Vomiting was minimized by withholding water and food by mouth as long as nausea was present or vomiting seemed likely to occur. Water or water with glucose was often given in small amounts (from 15 to 30 c.c. every fifteen to thirty minutes) when it was felt larger volumes might induce vomiting. (2) Deficit of water and electrolyte was restored by hypodermoclyses of physiologic saline or alkaline saline solutions.[7, 8] In some cases protoclyses were also used. (3) Intravenous infusions of glucose solutions were given to promote oxidation of glucose and to restore any possible deficit of available carbohydrate in the body. In most cases these procedures were considered sufficient to lead to recovery from dehydration, acidosis, and ketosis. However, in certain cases sodium bicarbonate was given by mouth when acidosis seemed so severe as to make it seem necessary to obtain prompt recovery of serum bicarbonate. In some cases insulin was administered in conjunction with glucose on the assumption (probably erroneous) that oxidation of glucose might be accelerated.

No systematic evaluation of the results of treatment can be given because of the heterogeneous character of the cases. Nevertheless, certain impressions concerning treatment can be brought out.

The recovery of the normal electrolyte pattern was quite prompt in most of the patients, as evidenced by subsequent examinations of the blood and by the clinical course. In twenty-four hours clinical improvement was marked, and the bicarbonate increased considerably but seldom reached normal values until treatment had been carried out for forty-eight hours. Attention is called particularly to Cases 1 A, 1 B, 4, 7, 18, 19, and 20, in which the greatest reductions in bicarbonate were found.

Sodium bicarbonate was given by mouth in Cases 1 A, 1 B, 16, and 18. In Case 1 A, 10 gm. divided in three doses was given between the first and second examinations of the blood. The child gained in weight from 10.1 to 10.8 kg., and the concentration of serum protein decreased from 8.09 to 6.40 per cent. The serum bicarbonate increased from 5.9 to 19.7 m.eq. per liter while the chloride increased from 117.4 to 123.4 m.eq. per liter and the ketone bodies remained the same. In other words, the recovery of serum bicarbonate was accomplished by the administered sodium bicarbonate while the remaining electrolyte remained about the same except for the increased volume of body fluid

indicated by the gain in body weight. The third blood sample shows that oxidation of the ketone bodies freed enough sodium for combination with carbon dioxide to raise the level of serum bicarbonate to 36.8 m.eq. per liter. No untoward symptoms accompanied this alkalosis, but reduction of serum bicarbonate was slow as is seen in the fourth sample taken a day later. A slightly high serum bicarbonate also resulted in Case 16 when sodium bicarbonate (2 gm. daily from March 7 to 11) was given by mouth. In Cases 1 B and 18, no alkalosis developed following the administration of 2.5 and 2.0 gm. of $NaHCO_3$ by mouth. While no harm was done in these cases, we feel that sodium bicarbonate is probably seldom if ever indicated in nondiabetic ketosis with acidosis. The use of alkaline saline or Hartmann's solution[7, 8] subcutaneously probably is somewhat more effective than physisologic saline. In any case subcutaneous saline solutions should be given in sufficient amounts to induce a diuresis. The slow recoveries in Cases 1 A and 4 were thought to be due to administration of inadequate amounts of saline solutions.

In Cases 1 B, 2, 4, 15, and 16 insulin was given in conjunction with infusions of glucose. The more rapid recovery in Case 1 during the second than the first admission was thought to be due to the prompt administration of an adequate amount of saline rather than the effects of insulin. In Case 16 insulin and glucose were given over a period of three days before the acetone of the urine decreased appreciably. Since we are accustomed to obtain more prompt results in diabetes, insulin does not seem to give the good results one obtains in true islet deficiency. The other cases in which insulin was used responded in much the same manner as the cases in which it was not used. The absence of hyperglycemia indicates that the use of insulin is irrational and unnecessary.

DISCUSSION

The group of cases of nondiabetic ketosis with acidosis presented in this paper brings out a number of factors, which, though not new, deserve more attention than has been given in the literature. Although ketonuria has been known to accompany a number of infections and other unrelated disorders, it is usually not appreciated that cases of marked acidosis are more frequently met in isolated attacks than in recurrent episodes. Since attention has been centered chiefly on cases of recurrent vomiting, the high incidence and severe character of ketosis in children younger than a year and a half is hardly mentioned in the literature.[9, 10] Gee[11] and others call attention to the fact that recurrent vomiting may start in infancy. Ketosis with acidosis in newborn infants has not been reported previously.

The frequency with which normal or high concentration of serum chloride was found in these patients is hard to explain if one assumes

that the vomitus contains normal gastric juice. Unfortunately the vomitus was not analyzed except in Case 3. This vomitus showed a normal excess of chloride over fixed base, but this finding may not be typical of ketosis with acidosis since this patient did not suffer from acidosis. During convalescence the gastric juice was normal on both admissions in Case 1. Knoepfelmacher[12] reported that the vomitus was acid early in the course of an attack of recurrent vomiting but later showed no free hydrochloric acid. O. Schloss found the vomitus to contain an excess of fixed base over fixed acid in some unpublished observations. The chemical findings in the serum indicate that patients showing ketosis with acidosis will probably frequently be found to vomit an alkaline juice.

Since it is appreciated that, when fat is burned without a simultaneous combustion of carbohydrate, ketosis develops, the theories of the pathogenesis of nondiabetic ketosis have centered about available carbohydrate of the body. Solomonson[1] summarized the work on recurrent vomiting and performed carefully controlled experiments of his own. He pointed out that, while starvation or a diet high in fat and low in carbohydrate tends to produce certain symptoms resembling an attack of recurrent vomiting, the fully developed picture has not been reproduced. These procedures were followed in some cases by vomiting, slightly enlarged liver, lowering of the blood sugar, and an increase in blood acetone, but the symptoms were never as severe as those of clinical cases. Similar induction of symptoms resembling those of recurrent vomiting have been reported by a number of workers.[12-17]

Ross and Josephs[16] noted an unusually low blood sugar content during a convulsion in a child subject to attacks of recurrent vomiting. Josephs[17] confirmed and extended the observations and brought out that certain children develop a greater lowering of their blood sugar after fasting for sixteen hours than others. However, subsequent observations[18, 19] showed that starvation in normal children produces fairly marked lowering of the blood sugar and that this hypoglycemia is not associated with unusual ketosis or tendency to convulsions. Weymuller and Schloss[15] found that a high fat diet produced a greater ketonuria in children subject to attacks of recurrent vomiting than in control children. They point out that no difficulty in storing glycogen exists (Levine and others[20]). One is left then with two suppositions to explain attacks of ketosis in nondiabetic children: (1) Glycogenolysis may be unusually rapid during starvation, fever, high fat diet, or other disturbances. Under these circumstances certain patients apparently do not produce sufficient carbohydrate from the metabolic products of proteins to prevent ketosis. (2) Certain circumstances may lead to rapid burning of fat per se or a difficulty in storing circulating fat (Weymuller and Schloss[15]).

Since glycogen is stored chiefly in the liver and since the liver is the organ contributing the largest amount of ketone bodies to the blood,[21] hepatic injury might be considered a likely lesion in pathologic ketosis. The frequency of enlarged livers in these patients may indicate hepatic lesions. However, diseases characterized by hepatic injury are not accompanied especially frequently by ketosis. Since the liver is apparently the chief site of formation of ketone bodies, any hepatic disturbance which explains nondiabetic ketosis probably does not affect this hepatic function. Furthermore, rapid burning of fat is accompanied by enlargement of and accumulation of fat in the liver. Autopsies in cases of recurrent vomiting are few[22, 23, 24] and fail to reveal characteristic lesions of the liver, though fatty changes were noted. Although vomiting, ketosis, hypoglycemia, and hepatomegaly in von Gierke's disease suggest certain analogies to the ordinary cases of nondiabetic ketosis, the ready response of the latter to infusions of glucose, as well as the lack of reports of accumulations of glycogen in the liver at autopsy, make it unlikely that temporary, defective glycogenolysis analogous to that of von Gierke's disease occurs during attacks of nondiabetic ketosis. For these reasons no conclusions can be made as to the significance of the high incidence of enlargement of the liver in nondiabetic ketosis with acidosis. Hepatomegaly may indicate a functional or anatomic disturbance of the liver, or it may merely signify unusually rapid metabolism of fat.

For the present, one is probably on safe ground in asssuming that *nondiabetic ketosis with acidosis is a potentiality in all children.* Little evidence exists that the recurrent or isolated attacks of ketosis with acidosis differ, except in degree, from what may be produced in normal children by starvation. However, one can scarcely doubt that some children, either because of their nervous make-up or a possible metabolic weakness, are more easily thrown into ketosis. Starvation due to vomiting is almost a constant contributing factor in cases with or without infections. Age is the most important predisposing cause since the frequency and severity of attacks of ketosis with acidosis is greatest in children younger than eighteen months. The specific effect of glucose orally or intravenously points to a deficit of available glucose as the probable immediate cause of nondiabetic ketosis. The deficit of carbohydrate may be due to exhaustion of reserves of glycogen or failure to metabolize sufficient proteins to supply glucose by glyconeogenesis.

SUMMARY

Serum electrolyte and clinical observations are reported on twenty cases of nondiabetic ketosis. Clinically, about one-third of the cases showed slight infections; one-third, moderate infections; and the remainder, severe infections. Only three deaths occurred, and in two

of these septicemia was the apparent cause; in the other fatal case no diagnosis could be made. In no case did acidosis per se lead to death. The type of infection did not seem to play a deciding rôle in the development of ketosis. The cases of severe acidosis occurred almost exclusively in infants aged less than eighteen months. Two cases with severe acidosis in newborn babies were described. Only three patients showed recurrent attacks of ketosis. Enlarged liver was almost a constant feature of the cases with marked acidosis. Recognition of the rôle of ketosis and acidosis in certain cases of severe infection leads to appropriate treatment and favorable outcome.

The reduction in bicarbonate was accounted for in some cases by accumulation of ketone bodies and in a few cases by increased concentration of chloride. Reduction in the concentration of total base (sodium) was not a prominent feature except in cases with severe infection. However, since dehydration was a prominent feature of the cases with marked acidosis, deficit of sodium and chloride was considerable. The blood sugar level was variable but did not show a consistent tendency to be unusually low.

Clinical experience, as well as the chemical findings in the blood, indicate that treatment should be directed toward stopping the vomiting, restoration of the deficit of extracellular water and electrolyte, and the administration of carbohydrate in order to insure conditions favorable to the combustion of glucose. Withholding food and water is frequently necessary on account of persistent nausea and vomiting. Intravenous infusions of glucose and hypodermoclyses of saline were apparently adequate for the restoration of the deficit of electrolyte and to combat acidosis. Administration of sodium bicarbonate by mouth led to considerable alkalosis in one case. This fact and the clinical course in other cases indicate that sodium bicarbonate is not necessary for the treatment of nondiabetic ketosis when sufficient physiologic saline or alkaline saline is given by hypodermoclyses.

CASE REPORTS

Case 1.—R. G. Recurrent vomiting; nondiabetic ketosis with acidosis.

The first admission (A) was Oct. 26, 1929, when the patient was fourteen months old. He had been ill for five days, starting with loss of appetite and repeated vomiting. Symptoms of acidosis developed the day before admission. The child was very sick, markedly dehydrated, showed Kussmaul breathing, with the odor of acetone to the breath. The pharynx was red. The liver was palpated at the level of the umbilicus, 4 cm. below the costal margin. The patient received a hypodermoclysis of 400 c.c. of saline and an intravenous infusion of glucose about twelve hours before the first blood sample was withdrawn. After the blood was withdrawn, the child received three doses of 3 gm. of $NaHCO_3$ by mouth. Treatment consisted of hypodermoclyses of saline, infusions of glucose, and blood transfusions. The child vomited a few times until the third day in the hospital. Thereafter nourishment was taken, and recovery was uneventful. On October 10, the gastric juice showed Cl, 57; total base, 86; and titratable acidity, 13.6 milliequivalents per liter.

Note especially that the acidosis was accompanied by high chlorides and fairly high acetone. In spite of the hypodermoclysis on admission, the child weighed the same (10.1 kg.) on the second day in the hospital. Adequate hypodermoclyses brought the weight up to 11.5 kg. on October 30. Treatment with sodium bicarbonate and hypodermoclyses led to recovery from dehydration and a normal bicarbonate, but ketosis persisted until October 30. With the oxidation of the ketone bodies, alkalosis, which was apparently symptomless, developed.

The patient was readmitted November 16, after being home for ten days. The child vomited repeatedly for four days before the second admission (B). Prostration and dehydration were less marked than on the first admission. The liver was felt 3 cm. below the costal margin. The boy was treated with 1,200 c.c. of saline subcutaneously, 60 c.c. of 20 per cent solution of glucose intravenously, and 2.5 gm. $NaHCO_3$ orally on the first day. Five units of insulin were given with the glucose. Twelve hours later the patient's weight had increased from 10.4 to 11.4 kg. and he looked much better. On November 11, the gastric juice contained Cl, 30; and base, 13 milliequivalents per liter. The more rapid recovery during the second admission was attributed to the prompt administration of adequate amounts of saline rather than the insulin.

The family moved to New York, where the patient was followed in the Cornell Clinic. In the fall of 1933 he was seen by Dr. Vernon Lippard, who found that attacks of abdominal pain and vomiting associated with respiratory infections had occurred. These took place irregularly about every three months; no fever was noted by the parents; no air hunger developed, and admission to the hospital was not necessary.

CASE 2.—S. R. (Colored.) Recurrent vomiting; malnutrition, nondiabetic ketosis with acidosis.

The patient was admitted to the hospital on Feb. 22, 1933, at the age of three and one-half years. In December, 1932, she suffered from moderately severe pertussis. Six days before admission she developed a cough and rhinorrhea. She vomited fourteen times on February 19 and showed ketosis when seen in the dispensary. Because she continued to vomit and failed to respond to treatment, she was sent into the hospital on February 22. On admission she was apathetic, undernourished, and showed Kussmaul breathing. The abdomen was scaphoid, and the liver was not palpated. Treatment consisted of hypodermoclysis of alkaline saline and infusions of glucose with insulin. Recovery was prompt with a gain in weight from 10.3 to 10.8 kg.

The patient was readmitted with a similar, but much milder, attack of vomiting and ketosis in September, 1933. No further attacks have occurred.

CASE 3.—R. G. Recurrent vomiting; nondiabetic ketosis.

The patient was admitted in July, 1928, at the age of three years, for an attack of vomiting which had lasted five days. He showed ketonuria and hyperpnea. No chemical studies were made. The patient thereafter was subject to a number of attacks of vomiting and ketosis which did not require hospital treatment. After vomiting for four days, he was readmitted Oct. 31, 1929, at the age of four years. Before admission the patient had been treated with orange juice to which NaCl had been added, but this was vomited. The face was flushed and the liver slightly enlarged. On admission analysis of the vomitus revealed Cl, 114; and total base, 67 milliequivalents per liter. He was treated with subcutaneous saline and intravenous glucose. Recovery was prompt. He was discharged November 4. There was no subsequent recurrence of attacks.

CASE 4.—H. C. Nondiabetic ketosis with acidosis.

The patient was admitted Sept. 14, 1930, at the age of fourteen months. He had suffered a little more than the usual number of respiratory infections during the first year of life. Two weeks before admission he passed three or four foul, loose, green stools. The diarrhea continued until admission. He vomited three times during the eighteen hours preceding admission. Heavy breathing was noted the day before admission. The diarrhea may have been precipitated by eating green grapes. On admission he was well developed and nourished. The cheeks were flushed, and Kussmaul breathing was present. Dehydration was only moderate. The abdomen was scaphoid, and the liver was felt 3 cm. below the costal margin. Treatment consisted of an infusion of 150 c.c. of 10 per cent glucose with four units of insulin. Improvement was slow but definite in twenty-four hours. No appreciable gain in weight occurred with recovery. It was felt that recovery was delayed by not using hypodermoclyses of saline.

CASE 5.—R. R. Nondiabetic ketosis with acidosis; congenital syphilis.

The patient was admitted to the hospital when he was one month old because of failure to gain in weight. A positive Wassermann reaction and signs of syphilis were found. In spite of treatment the blood Wassermann reaction remained positive, but the cerebrospinal fluid Wassermann reaction and colloidal gold curve were normal on fluid taken two days before present illness. The boy was admitted Aug. 3, 1934, at the age of five and one-half years. He had vomited repeatedly for the previous twenty-four hours. He was thin, moderately dehydrated, and looked fairly sick; the breathing was somewhat rapid and deep. The temperature was 38° C. on admission but normal thereafter. Subcutaneous injection of alkaline saline and intravenous infusions of glucose led to prompt recovery. He was discharged Aug. 9, 1934.

CASE 6.—L. deR. Poisoning with methyl salicylate; nondiabetic ketosis with acidosis.

The patient was admitted Aug. 24, 1932, at the age of two years. Three-quarters of an hour before admission the patient swallowed about 15 c.c. of oil of wintergreen. He vomited about one-half hour after being given milk. On admission a gastric lavage brought back a little mucoid material on which the odor of oil of wintergreen could be detected. The child did not appear ill. He was given an hypodermoclysis of 500 c.c. of saline and an infusion of 200 c.c. of 10 per cent glucose. Eighteen hours later he developed Kussmaul breathing, and the liver was palpated a little below the costal margin for the first time. Acetone as well as salicyl was detected in the urine. The temperature rose to 40° C. August 27, but was normal the next day. The patient was discharged well on Aug. 29, 1932.

The especial interest of this case lies in the development of ketosis within eighteen hours following ingestion of oil of wintergreen in spite of an infusion of glucose.

CASE 7.—G. S., newborn infant. Congenital maldevelopment of the brain, microcephalus; nondiabetic ketosis with acidosis.

The patient was born at term and weighed 3,200 gm. She was covered with meconium, and difficulty in getting her to breathe was encountered. The baby nursed poorly from the breast and bottle for the first two days and probably got little food or water. Twitching of the mouth was noted on the second day. On the third day she was transferred to the pediatric service because of dehydration and deep breathing. She received 250 c.c. of saline before coming to the pediatric ward where the sample of blood was obtained. The patient was markedly dehydrated and very sick. The liver was not enlarged. Under treatment with intravenous glucose, subcutaneous saline, and transfusions of blood recovery was prompt. She was dis-

charged when fourteen days old. Subsequently at the age of six months, she was found to be spastic, lacking in higher cerebral functions, and microcephalic.

This patient illustrates that marked ketosis with acidosis may occur in a newborn infant.

CASE 8.—A. L. Alimentary anemia; rhinopharyngitis; nondiabetic ketosis with acidosis.

The patient was admitted July 30, 1932, at the age of two years. He was a full-term baby who was weaned at seven months but thereafter suffered an attack of diarrhea and was fed a diet consisting chiefly of milk and sugar. No cod liver oil or orange juice was given. At one year of age he appeared pale. He had five convulsions during the second year of life. On July 16, 1932, he developed fever, rhinorrhea, and vomiting but seemed better two days later. July 29 the boy had fever, cough, and a convulsion. Another convulsion occurred on the day he entered the hospital. On admission the temperature was 40° C. The child was fairly well developed but showed marked pallor, moderate undernutrition, and stupor. Breathing was of the Kussmaul type. The pharynx was red, and the voice hoarse. The spleen was palpated 4 cm., and the liver 6 cm., below the costal margin. The leucocyte count was 32,000, and the erythrocytes numbered 4.8 millions per cubic millimeter. The hemoglobin was 26 per cent (Sahli). The patient was treated with infusions of glucose and a hypodermoclysis of saline solution. Recovery from acidosis occurred in twenty-four hours. Recovery from the anemia occurred in about two weeks under treatment with iron and an adequate diet. He was discharged Aug. 16, 1932.

CASE 9.—R. P. Congenital malformation of heart; occult spina bifida; nondiabetic ketosis with acidosis.

The patient was known to have a congenital lesion of the heart since he was one year old. He had been subject to attacks of bronchitis. During the three months preceding the present illness, he had several attacks of blueness lasting several days. Jan. 8, 1932, the patient developed cough and anorexia. Deep respirations were noted the day before admission. The patient was underdeveloped and poorly nourished. Respirations were rapid and deep, and an odor of acetone could be detected on the breath. Moderate cyanosis and clubbing of fingers was noted. The heart was enlarged, and a systolic murmur at the base was heard. The liver was felt 3 cm. below the costal margin. The temperature was elevated (38° to 39° C.) for a week. The ketosis disappeared within a day following intravenous infusion of glucose. A year later the boy died rather suddenly with probable heart failure. No necropsy was performed.

CASE 10.—L. R. Upper respiratory infection; nondiabetic ketosis with acidosis.

The patient was admitted Mar. 10, 1930, at the age of two and one-half years. He was taken ill rather suddenly with loss of appetite and vomiting on March 6. No vomiting occurred on the two days before admission to the hospital, but nothing was eaten on these days. On March 10 he became drowsy and on admission was moderately prostrated and showed Kussmaul breathing. The abdomen was scaphoid, and the liver was not palpated. Recovery from air hunger occurred in twenty-four hours following infusions of glucose and hypodermoclyses of saline. On the second and third days in the hospital the temperature was 39° and 40° C., respectively. No gain in weight occurred with recovery. He was discharged well on Mar. 20, 1930.

CASE 11.—D. B. Upper respiratory infection; nondiabetic ketosis.

The patient was admitted to the hospital Mar. 18, 1930, at the age of four years. He had been ill for three days with fever, prostration, and repeated vomiting. On

admission he was fairly sick and showed deep breathing. The patient recovered promptly after two infusions of glucose and was discharged Mar. 22, 1930.

CASE 12.—J. W. Upper respiratory infection; nondiabetic ketosis.

The patient was admitted to the hospital on Apr. 21, 1930, at the age of five years. She was taken ill April 17, with headache, malaise, and fever. The family physician thought the liver was enlarged at this time. From April 18 until admission, repeated vomiting occurred. On admission the girl was not very sick although she felt weak. The voice was hoarse, and the breathing deep. The patient was given a hypodermoclysis of 700 c.c. of saline; the first blood was taken eighteen hours later. Recovery was prompt. On April 23 a normal response was obtained to an intravenous sugar tolerance test. She was discharged Apr. 29, 1930.

CASE 13.—H. O'B. Capillary bronchitis; nondiabetic ketosis.

The patient, aged five years, was admitted to the hospital on Mar. 15, 1932. He was taken ill on March 13 with a persistent cough. Repeated vomiting and dyspnea developed the next day. On admission the patient was quite ill with fever (39.5° C.), prostration, hoarseness, and deep breathing. Moderate retraction of interspaces was noted, and diffuse, medium, moist râles were heard. The liver was not enlarged. No treatment was directed toward the ketosis. Recovery was rapid. Discharged March 23.

CASE 14.—M. W. (Colored.) Pneumonia (pneumococcus Type XXXI); nondiabetic ketosis with acidosis.

The patient entered the hospital June 9, 1934, at the age of two and one-half years. She had had a cold for one week and high fever for three days. She vomited three times the day before admission. On admission she looked fairly sick. The breathing was a little deeper than one would expect in pneumonia, and an odor of acetone could be detected on the breath. Signs of consolidatiton of the right middle lobe were found. The abdomen was normal. The liver did not seem large. The child's temperature remained elevated for three days in the hospitatl. On the second and third day in the hospital, the liver felt large (3 cm. below the costal margin), but the breathing no longer suggested acidosis. She was discharged June 22, 1934.

CASE 15.—J. R. Scarlet fever; mastoiditis; dehydration; nondiabetic ketosis with acidosis.

The boy entered the hospital on Apr. 8, 1932, at the age of three and one-half years. He became ill with fever and malaise on March 31. The next day he vomited once but seemed to be recovering until April 5, when he vomited repeatedly. On the next two days the vomiting continued, and a rash appeared. On admission to the hospital the boy was well developed though he had evidently lost weight. He was markedly dehydrated and almost moribund. The respirations were of the Kussmaul type. There was marked pharyngitis, cervical adenitis, and otitis media. The abdomen was scaphoid, and the liver was felt 2 cm. below the costal margin. The blood for chemical examination was taken before treatment, and, since the blood sugar was high, it was felt that the patient might be suffering from diabetes. He was treated with hypodermoclyses of saline and infusions of glucose with insulin. The recovery from acidosis and dehydration was fairly rapid (about forty-eight hours). Subsequently he developed desquamation suggesting scarlet fever. Mastoidectomy was performed April 23. Sugar tolerance was normal on April 16, and he was discharged well on April 30.

CASE 16.—R. Z. Scarlet fever; septicemia (*Streptococcus hemolyticus*); multiple subcutaneous abscesses; otitis media; dehydration; nondiabetic ketosis with acidosis.

The patient was admitted to the hospital March 4, 1930, at the age of three and one-half years. On March 1 he developed fever, vomiting, and restlessness. A scarlatiniform rash appeared on March. 2. Vomiting became frequent, and abdominal pain developed. On admission the boy was well developed and nourished, but acutely ill and greatly prostrated. Respirations were rapid and deep. The skin showed a typical scarlatinal rash. The pharynx was red and swollen; the cervical lymph nodes, large and tender. The lower lip showed an ulcer with surrounding inflammation. The abdomen was not distended but was tender over the right upper quadrant. The liver was felt 5 cm. below the costal margin.

The boy continued extremely ill for four weeks and the temperature did not remain below 38° C. until the sixth week. The boy seemed worse on the third day in the hospital. Blood cultures were positive for hemolytic streptococci for the first six days and twice thereafter, but they were negative after the tenth day. The breathing suggested acidosis for four days, and acetone was present in the urine for six days. Multiple subcutaneous abscesses developed.

The boy received scarlatinal antitoxin, blood transfusions, and infusions of glucose the first day in the hospital. Thereafter he was treated with repeated transfusions of blood, infusions of glucose, and hypodermoclyses of saline. From the third to the seventh day he received insulin together with the infusions of glucose. Decrease in the size of the liver was coincident with disappearance of acetonuria. He was discharged well on May 17, 1934.

CASE 17.—F. P. Enterococcal septicemia, peritonitis, pneumonia, otitis media, nondiabetic ketosis with acidosis.

The patient, one year old, entered the hospital on Feb. 14, 1930. He had had a cold two weeks before but seemed to be getting better until February 10, when fever recurred. On February 12 the respirations were labored; on February 13 the stools became loose and frequent, and he vomited; on the day of entry into the hospital diarrhea and vomiting were frequent. On admission the patient was well developed, but extremely ill, prostrated, and markedly dehydrated. The abdomen was not distended; the liver was felt 2 cm. below the costal margin. The baby was treated with hypodermoclysis of saline, infusions of glucose, and blood transfusion. Signs of pneumonia and peritonitis developed before death on February 15. No autopsy was performed. Cultures of the blood and peritoneal fluid revealed *Micrococcus ovalis*.

CASE 18.—E. L. Rhinopharyngitis, otitis media, bronchiolitis, bronchopneumonia, diarrhea, nondiabetic ketosis with acidosis.

The patient, aged one year, entered the hospital on Dec. 17, 1932. She became ill December 1 with cough, rhinorrhea, but no fever. She seemed to be recovering until December 5, when she vomited once. The next day she vomited after each feeding and passed twelve loose stools. The following day although she vomited but three times and passed but three loose stools, she looked much sicker and developed air hunger. On admission the temperature was 40°, and she showed marked Kussmaul breathing with an odor of acetone to the breath. Dehydration was very marked, sclerema being present. The abdomen was scaphoid, and the liver enlarged (2 cm. below the costal margin). The temperature remained 40° C. for three days and then varied between 38° and 37.5° C. for seven more days. The diarrhea continued for three days in the hospital. Although the serum bicarbonate became normal on December 9, the respiration remained rapid but suggestive of pneumonia rather than acidosis. Physical signs and a roentgenogram established the diagnosis of bronchiolitis and bronchopneumonia. Recovery from the infection was slow. She was discharged Jan. 12, 1933.

The baby was given nothing by mouth until the second day in the hospital when 10 per cent glucose was tried but was discontinued because of the vomiting. A mixture of skimmed milk plus dextrimaltose was started on the fifth day in the hospital. Hypodermoclysis of alkaline saline, infusions of glucose, and transfusions of blood were given during the first week. On admission 2 gm. of $NaHCO_3$ was given by mouth.

The patient has been followed in the dispensary through several infections without a recurrence of ketosis.

This patient probably suffered from an acidosis due to diarrhea as well as ketosis.

CASE 19.—Boy B. Newborn infant. Septicemia *(Streptococcus hemolyticus)*; bronchopneumonia, encephalomyelitis, nondiabetic ketosis.

The baby was born on Jan. 17, 1933, after a labor lasting nineteen hours and had to be resuscitated with artificial respiration and caffein. The body was covered with meconium. Six hours later facial paralysis was noted. Twelve hours after birth he vomited material containing blood, and the respirations were noted to be Kussmaul in type although periods of apnea occurred. Hypodermoclysis of 720 c.c. of saline was given during the first day. The extremities were spastic, and tremors and strabismus were noted the second day of life. On the third day of life acetone was detected in the urine and on the breath. Fever (38.9° C.) was present on January 19 and 20. The baby vomited repeatedly during the last three days of life. No note was made in regard to the liver.

Autopsy showed extensive necrobiosis, demyelinization and glial proliferation of brain; confluent focal pneumonia; pulmonary congestion and hemorrhages. The liver was large (175 gm.) but showed only fatty infiltration histologically.

CASE 20.—J. K. Nondiabetic ketosis with acidosis; cause of death not determined; anemia.

The patient entered the hospital on Oct. 4, 1930, at the age of eight months. Six weeks previously he had suffered for two days from a cold accompanied by vomiting. He was apparently well until October 1, when he vomited three times but seemed to have no fever or loss of appetite. He seemed better the next day though he vomited twice. The night before admission he vomited repeatedly and had two convulsions. On admission the temperature was 36.4° C. and the respirations were rapid (40 per minute) and deep. He was well developed but dehydrated and comatose. The abdomen was scaphoid, and the liver felt 5 cm. below the costal margin. The white blood count, 32,500; red blood count, 2.9 millions per cubic millimeter; hemoglobin, 58 per cent (Sahli). The temperature rose to 38° C. the next day and finally to 40° C. before death on October 7. He was treated by hypodermoclyses of saline, infusions of glucose, and transfusion of blood. He never recovered from the coma although the signs of dehydration and acidosis disappeared. The spinal fluid was negative. No autopsy was performed.

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ALLERGIC REACTIONS TO SCHICK TESTS AFTER TOXOID IMMUNIZATION

Report of Two Cases

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ALTHOUGH untoward reactions to the parenteral injection of foreign protein into the human organism have been reported by numerous observers, a careful survey of the literature fails to reveal any reactions resulting from the injection of an intradermal test dose of diphtheria toxin as used in performing the Schick test. In the present communication, we are reporting two such instances.

Case 1.—A twelve-month-old female infant with a past history of eczema was found, on Oct. 24, 1932, to give a positive reaction to the Schick test. One week later she received subcutaneously, 0.5 c.c. of diphtheria toxoid. Four weeks later she received a second injection of 1 c.c. of diphtheria toxoid. After four months the Schick test was repeated. Approximately fourteen hours following the intradermal injection of 0.1 c.c. of the standard dilution of diphtheria toxin, the child's skin became covered completely with urticaria. This persisted for hours. It was believed that an "anaphylactic" reaction resulted from the injection and that it was similar in mechanism to the reactions incident to a second injection of a foreign serum in a sensitized patient.

Case 2.—An eleven-month-old female, with a past history of eczema, was found to react positively to the Schick test on Nov. 15, 1932. Two weeks later she received 0.5 c.c. of toxoid. Three weeks later a second injection of 1 c.c. of toxoid was given subcutaneously, and three weeks later an additional injection was given. After eight weeks, Mar. 7, 1933, a second Schick test was made on the child's right arm. The child was frightened at the time and cried before, during, and after the procedure. Approximately two minutes later urticaria appeared on the child's face and soon extended over the body. At the site of the Schick test, a large wheal developed. The infant's eyelids became swollen, and edema of the face was followed by laryngeal stridor and cyanosis. Four minims of adrenalin chloride (1:1,000 dilution) were injected into the left arm while a tourniquet was applied tightly to the right arm above the elbow. In a few minutes the child appeared much relieved; the puffiness of the face subsided considerably; the cyanosis disappeared; the child breathed easily; and the urticaria rapidly faded. The tourniquet was released and within a minute all previous symptoms returned including moderately severe cyanosis. The tourniquet was reapplied, and adrenalin in the same amount was again injected into the left arm. The symptoms rapidly subsided. When the tourniquet was released once more, it was immediately reapplied, released, and reapplied again. This procedure involved several minutes. It is believed the urticarial reaction, as in the previous case, constituted an anaphylactic reaction due to a second intradermal injection of foreign protein.

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DISCUSSION

The mechanism of reactions such as this is not entirely understood, but in light of the present knowledge of allergy it may be explained on the basis of a state of hypersensitiveness induced by previous injection of the specific protein. The possibility of repeated injection of toxin-antitoxin producing a state of hypersensitivity to horse serum in individuals has been discussed by several observers.[1, 2, 3, 4, 5] However, since horse serum is not present in either toxoid or diphtheria toxin diluted for the Schick test, the reaction seen in the two cases mentioned certainly could not have been due to sensitization to horse serum. A plausible explanation, we believe, would be that a previous Schick test followed by toxoid injections sensitized these infants to the bacterial protein, the bacterial toxin, or the protein in the culture medium used in the production of the toxin.

A similar hypothesis was offered by Sugg, Richardson, and Neill[6] in their communications. They report evidence that diphtheria toxin can function as an antigen in the production of anaphylaxis. In view of the facts that both children were eczematous and that in numerous other cases no such reactions have occurred, we may conclude not only that such reactions are rare, but also that they possibly may occur only in hypersensitive types of children.

In view of these two experiences it is felt that certain precautionary measures are indicated. First, such reactions, although extremely rare, probably should be borne in mind, and methods of combating them should be available. Such methods include the presence of adrenalin chloride and the knowledge that a tourniquet tied tightly enough to stop the pulse will prevent rapid dissemination of the injected material. This latter procedure, emphasized by Duke, may be of greater importance than the injection of adrenalin chloride. Waldbott[7] refers to this procedure, which he found more efficacious than atropin or adrenalin chloride in combating reactions to injections. Another precaution offered is that in sensitive children the injections of toxoid be spaced more closely together than three- or four-week intervals. A third precaution would be to repeat the Schick test in sensitive children after six months, instead of six weeks, following the last injection of toxoid, thus avoiding a possible state of extreme hypersensitivity. Finally, in repeating the Schick test in children who are known to be allergic, it may be advisable to do a preliminary skin test with a dilution (perhaps 1:200) of the Schick material.

CONCLUSION

Hypersensitive individuals may become sensitized to the bacterial protein, toxin, or broth proteins in toxoid so that a Schick test made after toxoid injections may result in an anaphylactic reaction.

A tourniquet above the point of injection adds greatly to the relief of anaphylactic symptoms.

A skin test with diluted Schick toxin would appear to be indicated before a Schick test is made on an individual of the hypersensitive type who has received toxoid innoculations.

It is possible that emotional disturbances, particularly fright, may play some part in the precipitation of these anaphylactic reactions.

Such reactions, as reported here, are extremely rare and should not nullify proper preventive or prophylactic measures.

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Critical Review

INFECTION AND IMMUNITY: PASSIVE IMMUNITY IN CONTAGIOUS DISEASES

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IN A previous article the fundamentals of immunity and infection were reviewed.[1] This issue contains the report of a committee appointed by the Academy to consider the methods of active immunization employed in contagious diseases. A corollary to this report would be a commentative review on the methods of passive immunization.

Some general points about passive immunity should be stressed. Passive immunization is only temporarily beneficial, since it only tides the patient over a crisis caused by some specific element. It is usually specific for only one organism, either for its exotoxin, endotoxin, or bacterial fraction; it plays no part in repairing organs that have been previously damaged by the specific element; it is ordinarily found in the serum obtained from a human being or another species that either has had the disease or that has been actively immunized against the specific infection by artificial means.

Practically all serums used to immunize human beings passively are obtained from human beings or animals, i.e., the horse, sheep, or goat. Animal serums are prepared by commercial firms who must meet the strict requirements of the United States Public Health Service and are frequently checked by the government. This is not true of human serums; hence, one should investigate the source of any human blood plasma used in passive immunization. Such serums should be obtained from individuals who are negative reactors to the Wassermann test and who have no signs of tuberculosis or active disease of any kind. These serums should be inactivated at 56° C. for one hour before bottling, and a preservative should be added before storing. Some workers pass the material through a filter, add a preservative, and then store. All serums should be examined from time to time, and those that have become clouded or show signs of contamination should not be used. It is getting more difficult for the practicing physician to obtain convalescent human serums since most of the men who have the responsibility of preparing them hesitate to take the hazards of a chance infection that might result from any latent bacteria that might be present in serums that come from their laboratories. Although the average practitioner cannot carry out the procedure described in the foregoing, he can bleed a patient who is convalescing and allow the blood to flow into a citrated syringe. He can then inject the whole blood directly into the muscles of the patient to be passively immunized. One need not worry about blood

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matching when injections are made intramuscularly. Even with intramuscular injections, the plunger of the syringe should always be withdrawn after piercing the skin and when it is in situ to see whether there is any bleeding which would signify that a vessel had been entered. If the amount of blood to be injected at any one time is large, it should not all be delivered in one spot; this applies to commercial antitoxins as well. The injection of any material, even though it may be of a homologous source, is a foreign body and absorption must take place through an inflammatory reaction in which the white blood cells play a prominent part. If too much serum is injected into the muscles of one area, it is possible for a sterile abscess to develop, which may have to be surgically evacuated. Neither should the injection of serum or antitoxin be made subcutaneously since there will be same delay in absorption; if this goes beyond seven or eight days following the injection, a localized inflammatory reaction may occur and sloughing of the tissues follow, a sort of modified Arthus phenomenon. Serums and antitoxins should never be given subcutaneously, if for no other reason than to avoid the pain which follows such a method of injection.

When antitoxins are given, one should expect a certain percentage of the patients to have serum reactions. These are termed as immediate, accelerated, and late[2] (see Table I). The percentage of these reactions

TABLE I

Immediate Reactions:

(1) Fever with chills; (2) pulmonary evidence; (3) generalized itching; (4) generalized urticaria; (5) nausea and emesis; (6) any of the above associated with cyanosis, dyspnea, vomiting, convulsions, sneezing, gastrointestinal symptoms, unconsciousness, modified shock or arthritis.

Accelerated Reactions:

The same types of reactions described above appearing within a few to forty-eight hours after the injection of therapeutic serum.

Late Reactions:

Generalized urticaria alone or with arthritis, adenitis, gastrointestinal symptoms, and fever.

depends upon the manner of administration and the type of antitoxin. There is a high rate of immediate reactions following the intravenous injection of antitoxins. In general, intramuscular injections are the safest from the standpoint of the practitioner. Homologous serums (convalescent serums) if injected intramuscularly give but few reactions other than fever and an occasional maculopapulated sparsely distributed, but generalized rose red rash which comes on from seven to fourteen days after the injection.

The method of testing the value or efficacy of any passive immune principle, either serum or antitoxin, is by animal experimentation or by clinical experience. The number of diseases, the specific element of which may be conclusively tested by animal experimentation, are few indeed. Thus it follows that clinical experience is the only way to judge the efficiency of a therapeutic procedure. With no measurable method of comparison, differences of opinion are bound to arise as to the value of any particular method of passive immunization.

The clinical reasons usually given for employing passive immunization are that after its use the mortality rate is decreased, the patients feel better subjectively, the temperature drops, the pulse rate decreases, the period of convalescence is shortened, and the number of complications is fewer.

In our enthusiasm, however, we forget that often the patient dies from some cause other than the disease which started the process; that the employment of passive immunity may defeat the establishment of any permanent active immunity; that one epidemic of disease may be extraordinarily virulent and another mild in character; that every infection has its own natural history and that most acute diseases are self-limited anyway. It follows that it is difficult to evaluate the efficacy of a therapy used in such diseases. It is twice as difficult if the mortality rate is low and the disease is one which cannot be given to animals.

Measles.—[5-8]Intravenous injections or transfusions of properly matched adult human blood (from 100 c.c. to 250 c.c.) or injections of convalescent measles serum as high as 50 c.c. intramuscularly are recommended for treating individuals ill with measles. The mention of any and all serums made from organisms (Ferry and Fisher, Tunnicliff, Caronia) or viruses (Degkwitz) that have been described as the specific causes of this infection is avoided, since such causative factors have not been accepted yet as proved etiologic agents. Transfusions or intramuscular injections of adult whole blood may be of some general benefit, but, since it has been recently shown that adult serum does not prevent susceptible children from contracting measles after exposure, it would appear that its therapeutic use would be equally doubtful. However, no harm is done and some general benefit may be gained from such a procedure. Even the efficiency of convalescent serum itself has been doubted. It is physically impossible to protect everyone, but it might be worth while to protect passively physical weaklings.

Mumps.—From 10 c.c. to 40 c.c. of convalescent serum has been recommended to prevent orchitis. It is difficult to draw any conclusions since practically all patients recover from mumps and the complication rate is variable. The most one could say is that the injection of convalescent mumps serum is harmless.

Chickenpox.—The injection of convalescent serum as a therapy for chickenpox would seem like a wasted effort since the complications of this disease are so few and the mortality rate negligible.

Whooping Cough.—[9-13]Two procedures of treatment have been suggested, i.e., (1) whooping cough vaccine (Sauer) or endoantigens (Krueger) in the early stages of the disease and (2) convalescent whooping cough serum for the severely ill patient.

At first, one would be inclined to object to the injection of a specific element during the incubation period of an infection, since it might act in a synergistic manner and aggravate the disease. If one examines the reports in the literature and analyzes the personal experiences of men specializing along this line, it is clear that no matter what it accomplishes, it does not seem to aggravate the illness. One must likewise conclude that there is no conclusive evidence that such a therapy modifies the disease, although it might still be used on the basis that it might do some good, especially, since it does no harm.

Convalescent whooping cough serum has been recommended for the severely ill patient. Little is written on this specific point and it is difficult to draw conclusions. Recent work has tended to show that the antigen of the bacillus is not neutralized by convalescent serum but that the local reaction following the injection of a combination of an antigen and serum is actually accentuated. One would therefore be tempted to question the use of convalescent whooping cough serum. Nevertheless, I have never heard of any accidents due to the use of such a serum. If I did use it, I would give it early in the course of the disease. It would seem worthless to give it late since the majority of deaths in whooping cough are caused by the effects produced by secondary invaders.

Scarlet Fever.—[14, 15]The reviewer previously analyzed the literature on the benefits of passive immunity in scarlet fever. The literature that has appeared subsequently has not caused him to alter his opinion.

"In my experience, I have had all types of reactions—early thermic responses, thermic responses with urticaria and edema, late urticaria and an anaphylactoid phenomenon with three deaths due to, or hastened by, antitoxin. In most of our treated cases there was far more illness from the effects of serum sickness than from the scarlet fever. Is it worth while, then, to inject all our patients in the face of the mildness of the present type of scarlet fever, just to see them better a day or two sooner and have serum sickness, or would it be better to leave them alone and take our chances on the average course of the disease? I believe that all will agree that the ultimate fate of antitoxin therapy will be settled only in an epidemic with a high mortality rate. I myself have yet to see the data of a series treated with intramuscular injections of scarlet fever antitoxins which I could not, without much discredit, match with a series of my own untreated cases."

Personally, I have a great deal of faith in human convalescent scarlet fever serum and use it in the same manner as other serums, i.e., from 50 c.c. to 100 c.c. intramuscularly, etc. If it is not available, however, and in a severely toxic case, I would certainly use antitoxin on the theory that it might do some good.

Diphtheria.—[16-23]This is a disease for which we have a definite antitoxin, both preventive and curative if given early enough and in sufficient quantities, and yet the mortality rates average from 10 per cent to 15 per cent. To understand this, it must be remembered that the disease is an "anesthetic type" of infection, one that does not worry the parents until it is often too late. It likewise must be realized that this is an infection which produces its damaging effects only when its toxin gets into the blood stream and that any damage done to various organs before antitoxin is administered is repaired by nature only. All that antitoxin does is to destroy or to neutralize the free or uncombined toxin. There is likely to be more cardiac complications since the use of antitoxin than there were before its use became general, because antitoxin now saves many individuals with damaged hearts who previously would have died with the infection.

Some general rules regarding passive immunization for diphtheria should be emphasized. Enough antitoxin should be given subcutaneously, intramuscularly, intraperitoneally, or intravenously at the onset and in but one injection, if possible. The reviewer has previously stated

that any antitoxin—and this includes diphtheria—should never be given subcutaneously, not only because of the pain that follows, but also because absorption is slow and a localized Arthus phenomenon may develop. Whether it should be given intravenously depends on the blood pressure. It is a waste of time to inject individuals with antitoxin either intraperitoneally or intramuscularly if the blood pressure is so low that there is not enough peripheral vascular circulation to absorb it. Antitoxin can be given intramuscularly to any patient with a good blood pressure, and it is less likely to cause reactions. Various amounts of antitoxin have been recommended in articles and texts—from 1,000 units to 5,000 units for infants and children and from 2,000 units to 300,000 units for adults. Twenty thousand units of concentrated antitoxin will be absorbed from the peritoneal cavity of a 250 mg. guinea pig within twenty-four hours; therefore, one need not worry much about the use of too much antitoxin in infants. From a practical standpoint, it would seem better to forget about the age, sex, and weight, of a patient and give the mild and moderately ill patient 20,000 units intramuscularly and those who are severely ill and who have a lowered blood pressure 40,000 units intravenously. It may be that these doses will have to be increased, since from European sources has come information about recent epidemics of diphtheria caused by a more virulent form of the organism, the so-called diphtheria gravis. It is well to use massive doses of antitoxin in severe fulminating infections that appear to run counter to our average experience. It has been shown that the toxin of the gravis organism is more virulent than that produced by the ordinary Park No. 8 bacillus. The latter is used to make antitoxin in this country. Park No. 8 antitoxin can neutralize diphtheria gravis bacillus if enough is given. In cases that appear to be malignant, large doses of antitoxin, as high as 100,000 units or more, are indicated.

Epidemic Meningitis.—[24, 25]Antimeningococcus serum is used for passive immunity. This is not an antitoxin, but a serum with bacteriostatic or bacteriocidal qualities. Recently a soluble toxin of meningococcus was described, and some effort is now being made to produce a serum that is both bacteriocidal and antitoxic. This may be of some value since the mortality with this infection is high in spite of the use of specific serums. Innumerable articles have been written about the therapeutic results obtained with the use of antimeningococcus serum, and from these it is apparent that the fulminating toxic type of disease is usually not very amenable to any treatment and the patients die within from six to forty-eight hours. Often the diagnosis is not even suspected until some other patient begins to show the usual picture of a relatively more chronic type of meningitis (relative in the sense being a matter of a few days). Ignoring the infant and toxic fulminating types, the mortality rate may be as low as 15 per cent in certain series of cases treated with antitoxin.

If there is going to be any improvement, it should occur promptly. Since this disease is notorious for its relapses, it is advisable to taper off the treatment over a number of days in order to avoid the possibility of shock in case there is a relapse and serum has to be given again (usually from seven to fourteen days after the last treatment). One should be careful not to mistake the meningeal serum sickness re-

action, occurring from about seven to fourteen days after treatment ends, as an exacerbation of the disease since further specific treatment in these cases would aggravate the condition.

Smallpox.—There is no need for any therapeutic serum since active immunization properly applied is 100 per cent protective.

Poliomyelitis.—[25, 27-32]The serum has yet to be described that will prevent the disease from developing in the monkey injected with the virus, although some serums have prolonged its life a few days. Theoretically, in the human being, convalescent poliomyelitis serum should be given in the preparalytic stage, but usually the diagnosis is not made until there is frank paralysis. Whether convalescent poliomyelitis serum will stop the spread of paralysis is questionable. Recent surveys were not conclusive as to its value, but, since it does no harm and might do some good, there is no definite contraindication to its use. From 10 to 20 c.c. of serum may be given intramuscularly, although recent articles indicate that larger doses would be more effective.

Erysipelas.—[33-37]Erysipelas is one disease the natural history of which ought to be studied before conclusions are drawn about the beneficial effects of therapeutic antitoxins. Most of the articles written about the results obtained after the use of erysipelas antitoxin may be variously interpreted.

The personal opinion of the reviewer is that the antitoxin is not of much value save in the treatment of infants. There is, however, this comforting thought, that the patients with erysipelas tolerate the injection of this antitoxin well and relatively few of them have serum sickness. It does not seem to harm the individual, and it might do some good.

Encephalitis.—A principle of passive immunity has not been developed for this disease as yet.

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American Academy of Pediatrics

FOURTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CLEVELAND, JUNE 11, 1934

Round Table Conference on the Newborn

Leader: Dr. Arthur H. Parmelee, Oak Park, Ill. Assistant: Dr. H. N. Sanford, Chicago, Ill.

CHAIRMAN PARMELEE.—This morning's round table discussion is to be on the subject of the newborn, with special emphasis on respiratory and circulatory disturbances.

We are all interested in increasing our knowledge of the newborn for the purpose of applying that knowledge in lowering the mortality of the hazardous period of transition from intrauterine to extrauterine life.

The newborn infant must rapidly adjust himself to many profound anatomic and physiologic changes. This adjustment, complicated and difficult as it must be under the most favorable conditions, becomes all the more difficult because of the traumatic insults of the birth process from which no infant can entirely escape.

The ability of the infant to make these physiologic and anatomic adjustments will depend largely upon three factors: (1) the inherent vitality, (2) the degree of maturity at the time of birth, and (3) the extent to which pathologic conditions disturb the normal course of events.

The problems of respiration and circulation in these infants are two closely related functions and can hardly be dealt with separately. Difficulties encountered by the newborn in adjusting himself to his new mechanism of gaseous exchange will affect, and in turn be affected by, the adjustments going on in the circulatory system.

The physiologists, embryologists, and anatomists have busied themselves with these problems and have in some instances taken us to task for our ignorance. Many clinicians have also made valuable contributions to our knowledge of these vital phases of the newborn infant's adjustment. I shall attempt to outline briefly some of the features which seem to me of practical importance, but, as I do so, I should like to have you keep in mind that in our clinical work we are dealing with individual infants. The ability of each individual infant to make his adjustments depends not only upon what may be proved to be a normal physiologic response to certain stimuli, but as well upon the three factors mentioned above, i.e., the inherent vitality (constitution), the degree of maturity, and the pathologic conditions that may be present to disturb the normal course of events.

The Initiation of Respiration.—Respiratory activity begins, under normal conditions, almost simultaneously with the birth of the infant. That the initiation of

respiration is due to stimulation of the respiratory center and that CO_2 is the chief stimulant material is generally conceded. But the factors which govern the action of the stimulus are numerous, and the explanation of disturbances of respiration is a complicated one.

Schmidt says that the chief element in the chemical regulation of respiration is the concentration of the stimulant material within the cells of the respiratory center. This, he says, is dependent upon a balance among three factors: the concentration of the stimulant material in the arterial blood; the rate at which stimulant material is produced within the cells of the center; and the rate of blood flow through the center, which rate determines the extent to which stimulant material can accumulate there. That the respiratory center is influenced directly by changes in its blood supply and that respiratory response to changes in systemic blood pressure depends chiefly upon changes in cerebral blood flow have been experimentally proved. Normally an increase in cerebral blood flow depresses respiration, and a decrease stimulates respiration. This suggests that products of metabolism of the cells of the center play a part in regulating the activity of the center. But there is an abnormal condition of the center in which respiration is depressed by a decrease in its blood supply and stimulated by an increase. This abnormal relation is designated the "reversal."

Apparently the ability of the respiratory center to respond to stimuli depends upon a supply of oxygen adequate to support the metabolic processes upon which the functional activity of the cells depends. The reversal cannot be produced by an excess of CO_2 in the blood as long as the blood oxygen content is not markedly reduced and the cerebral circulation is adequately maintained; but it is readily produced by a general anoxemia or by a reduction of the cerebral blood flow. Schmidt says that any agent normally a stimulant to respiration may cause depression or failure if applied in the presence of oxygen deficiency in the brain consequent to subnormal cerebral blood flow.

These observations led Krafka to the conclusion that the apnea of intrauterine life is due to the phenomenon of reversal produced by a physiologic anemia. He suggested also that occlusion of the umbilical arteries by increasing the peripheral resistance raises the systemic blood pressure and increases the cerebral blood flow. This relieves the apnea; the high carbon-dioxide concentration prevailing acts as a respiratory stimulus; and respiration is initiated.

In an excellent summary of his experimental work Schmidt makes the following statements: "The chief function of the entire respiratory mechanism is the maintenance within the center of a constant concentration of stimulant material. Factors known to be concerned in this maintenance are: changes in arterial blood, through changes in pulmonary ventilation, acid excretion by the kidneys, etc.; changes in the metabolic activity of the center, possibly concerned in the irritability of the center and in the reflex regulation of breathing; changes in the blood supply of the center, through local vascular and general vasomotor responses, which influence removal of metabolites from the center. Respiratory activity at any instant depends upon a delicate equilibrium among these factors and can be altered by changing any one of them."

Continuing, he says, "The nature of the stimulant material responsible for the regulation of respiration cannot be determined until more definite information is available concerning the part played by changes in the vessels supplying the center. The material is derived from the metabolism of cells, including those of the center, and it is probable that CO_2 is more important to the normal regulation than oxygen lack because the latter tends to modify the activity of the center by producing the reversal."

Asphyxia of the Newborn.—According to Seitz, 3.5 per cent of all infants are born in a condition of deep asphyxia. While some cases of asphyxia are due to local obstruction to the air passages, the majority result from a depression of the respiratory center.

The factors involved in this state of depression have been discussed. In the premature infant we have the additional factor of immaturity of the respiratory center. The significant part played by intracranial injury in the etiology of severe asphyxia is well recognized, and the remarks already made concerning the factors regulating respiration help to make this understandable.

In premature infants asphyxia at birth is, according to Yllpö, no more frequent than in full-term infants. Its etiology is the same as for full-term infants plus the factor of immaturity of the central nervous system. A peculiar type of breathing called "periodic breathing" is said to be physiologic for premature infants. It has been produced experimentally by primary changes in the blood supply of the center. The unstable vasomotor mechanism of the premature infant is probably an important factor in the occurrence of this phenomenon. Räihä and Salami, pupils of Yllpö, have expounded the theory that the high hemoglobin content of the blood in the newborn and especially in the premature may play a part by binding more oxygen and thus reducing the amount of stimulant material in the blood. Oxyhemoglobin is a stronger acid than is reduced hemoglobin, and the more oxyhemoglobin in the blood the less CO_2 is it able to bind.

In the premature infant we have also an asphyxial state which develops in the second or third week of life, or even later. The explanation of this condition is not yet satisfactory. According to Ekstein, the autopsy findings are inconstant and not characteristic, sometimes including cerebral hemorrhage and only now and then atelectasis of any degree.

A functional inferiority of the central nervous system, which does not produce symptoms until a certain stage of development is reached, suggests itself. However, there are probably many other factors. The weakness and eventual fatigue of the muscles of respiration may play a rôle.

Atelectasis.—In medical literature and in medical parlance generally, there is much loose talk about atelectasis. A rather thorough consideration of this subject, so that we may have some degree of uniformity in our conception of atelectasis, would seem to be very much in order. I believe we are well agreed that the lungs of the normal full-term infant undergo gradual inflation during the first few days of life and that during this time a variable amount of initial atelectasis is present in all normal newborn infants.

This, if our belief is a fact, can rightfully be called "physiologic atelectasis of the newborn." Physiologic peculiarities of the newborn sometimes take on pathologic proportions. This is true in regard to atelectasis. Various hindrances to the respiration of the newborn may result in the persistence of atelectasis to a pathologic extent. The persistence of large areas of atelectasis may be an important factor in causing death. However, more important for us is a knowledge of the factor or factors that cause the atelectasis.

Besides this primary type of atelectasis, there are secondary types—resorption atelectasis, for example, in which areas of lung that have been inflated become obstructed due to some hindrance to normal respiration and the alveoli collapse as the air is resorbed from them. Yllpö among others believes that primary atelectasis even in the premature infant is comparatively rare and that a secondary type is much more common. In the premature infant he maintains that nearly all of the small alveoli are inflated within a few hours after birth but that they soon become filled with blood constituents through exudation resulting from passive congestion.

The peculiar tendency to edema in premature infants is responsible for water-logging of larger or smaller areas of the lung. The increasing weakness of the heart becomes an important factor; as atelectasis increases, a greater load is put upon the pulmonary circulation, making in turn still greater demands upon the strength of the heart, and thus a vicious circle is created.

The recent publications by Farber and Wilson on the subject of atelectasis in the newborn handle the subject in a very sane and thorough manner. They claim it is possible by microscopic examination of lung tissue to determine accurately whether the atelectasis found is primary or secondary. The cuboidal cells lining the alveoli of the lung become flattened when the alveoli are inflated and remain flattened even if the air is resorbed.

In discussing atelectasis in premature infants, they say: "Any of the types of atelectasis described may be found in the premature as well as in full-term infants. However, in addition to these types of atelectasis, there may be present in the lungs of premature infants, solid areas of parenchyma superficially resembling atelectasis, but explained by incomplete development or immaturity of these areas. This finding does not represent true atelectasis."

The problem of atelectasis is concisely summarized by these investigators as follows: "The diagnosis of this condition as a complete and satisfactory cause of death, especially in premature infants, is widely accepted. It is obvious that when large areas of atelectasis are found in the lungs of a newborn infant who has died after exhibiting such evidence of imperfect respiratory function as constant or intermittent cyanosis, there must be a relation between the atelectasis and the anoxemia. The atelectasis may be accepted as the immediate cause of the anoxemia. As long, however, as the lung is anatomically perfect, it is not logical to accept the existence of atelectasis as a satisfactory explanation of death; on the contrary, the atelectasis should be considered due to more fundamental causes and its pathogenesis more thoroughly considered."

They then enumerate the factors preventing the initial normal expansion of the newborn baby's lung. Cohesion of the moist surfaces of the air passages in collapsed and airless lungs offer considerable resistance to the entrance of air. This initial resistance of the atelectatic lungs to expansion is always present and contributes to the maintenance of atelectasis to a pathologic extent when it is combined with any of the following factors: an imperfectly developed or an injured respiratory center; a poorly developed thorax as is seen especially in premature infants; bronchial obstruction due to aspiration of the contents of the amniotic sac, mucus, or blood. In regard to this latter factor Reuss believes that the irritation of the mucous membranes caused by aspiration of amniotic fluid gives rise to a prolonged catarrhal secretion and that this "amniotic mucus" is more important in causing obstruction than is the original material aspirated. This is especially true if the cough reflex is insufficient.

The Circulation.—It is a habit of authors of textbooks, in order to make their books complete, to copy from older textbooks certain statements which they consider authentic. Thus we have been passing on decade after decade teachings that should have been revised in view of the accumulation of new facts. This seems to be the case in regard to the fetal circulation and the changes that occur after birth.

Patten has brought this to our attention, albeit in a rather caustic way. I doubt if any of us still believe in the doctrine of Sabatier, promulgated in 1791 to the effect that the entire inferior vena caval stream passes directly through the foramen ovale into the left atrium with little or no mixing with the blood from the superior vena cava. I think we are all aware of the experimental work done by Pohlman in

1909 showing that mixing of superior and inferior caval blood occurs in the right atrium. We might not know, but we are glad to learn that Kellogg verified Pohlman's experiments in 1928.

I wish to call your attention to Patten's work which, if true, will give us a new attitude toward the circulation in the fetus and in the newborn. He has shown that the apparent capacity of the foramen ovale of the fetal heart is greatly reduced by the manner in which the valvula is attached to the septum and that the effective interatrial passage in the heart of the full-term fetus is a scant half of the size of the foramen ovale and little more than 40 per cent of the size of the inferior caval orifice. Because of its small size, the foramen ovale cannot pass on to the left side enough blood to equalize intake on the left with intake on the right. In view of the fairly equal development of the two sides of the fetal heart, any assumption that they do not handle approximately equal amounts of blood is untenable.

The neglected factor in the situation is the pulmonary circulation. All the implications are against the current view that the pulmonary circulation is negligible. The actual size of the pulmonary veins indicates that they bring into the left atrium a volume of blood somewhat greater than that contributed by way of the restricted functional orifice of the foramen ovale. These facts make it necessary to change our previous theory of an abrupt increase in the pulmonary circulation at the moment of birth. He measured the size of the pulmonary arteries, the umbilical arteries, the pulmonary veins, and umbilical veins and concludes that, if the pulmonary vessels are carrying a circulation in any way consonant with their size, there is enough blood already going to the lungs before birth to care for oxygenation as soon as the lungs are inflated. In regard to the postnatal changes in circulation, he discredits the idea that there is any marked or abrupt change in the relative pressure in the two sides of the heart when placental circulation is interrupted. He says: "As far as the heart is concerned, the immediate result of tying off the umbilical vessels is merely to eliminate from the fetal circulation the blood that happened to be passing through the placenta at that moment. It can have no more effect on relative pressure in the two atria than loss of the same amount of blood by superficial hemorrhage."

The establishment of an adult type of circulation is accomplished gradually. All the primary readjustments appear to be fairly well accomplished by the end of the first month or six weeks. The final steps are then taken in a leisurely fashion.

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DR. HEYWORTH N. SANFORD (CHICAGO).—Dr. Parmelee has outlined the mechanism whereby the respiratory stimulation necessary to establish normal respiration at birth is begun. Asphyxia neonatorum is, therefore, a failure for some reason of this normal stimulation to begin naturally.

The etiology of asphyxia neonatorum has been classified by McElroy as follows:

I. Intranatal causes
   A. Suffocative
      1. Compression of the uterus
      2. Interference with the umbilical circulation
      3. Interference with the placental circulation as in such diseases as toxemias from syphilis, chronic infections as nephritis, and heart disease, and acute bacterial infections. All these reduce the normal blood supply by placental infarcts.
      4. Prematurity, by predisposing to prolapse of the cord, and head injuries, and by faulty development of the respiratory mechanism
      5. Drugs: anesthetics, such as morphine, pituitrin, and ergot
   B. Paralytic
      Cerebral hemorrhage from forceps, breech presentations, and long labors

II. Postnatal asphyxia
   A. Injury to the head or cord by delivery methods
   B. Forcible methods of resuscitation that aggravate preexisting conditions.

The symptoms are usually stated in obstetric textbooks as falling into two main groups. Roughly, asphyxia livida is almost always due to the suffocative type and is the result of the aspiration of mucus, amniotic fluid, blood, or meconium. The infant is cyanotic, although the lips are pale. The general muscle tone is rigid, and there is a rapid response to stimulation. The second type, asphyxia pallida, is almost always due to the paralytic type of etiology. With this the child is white and flaccid, and there is little or no response to stimulation.

In the actual diagnosis it is not possible in the presence of immediate asphyxia to go into much detail. Roughly, we have asphyxia if cyanosis is persistent, intermittent, or tardy. A weak or grunting cry with shallow respiration usually indictates a cerebral hemorrhage. Occasionally with intensive atelectasis the percussion note is dull, the breath sounds are decreased, and râles are heard over the atelectatic area. Unfortunately these are not found in every instance—enough to make a positive diagnosis. Dunham has drawn attention to the x-ray as a means of differentiating atelectasis from other forms of lung pathology, such as pneumonia, pneumothorax, thymic enlargement, cysts, emphysema, and diaphragmatic hernia.

In the treatment I have thought it best to take up in detail the various measures in vogue, with the arguments for and against their use.

1. *Body Manipulations.*—Such procedures as the Schultz maneuver and the like have long been in vogue by obstetricians and are still to be found in practically all obstetric textbooks. These vary from massaging the skin and slapping the child to vigorous swinging in the air. These methods are more notable for their spectacular violence than the results obtained, and they are now generally condemned. They undoubtedly account for the unnecessary death of many babies each year.

In the presence of intracranial injuries such procedures are even more dangerous. Crothers has pointed out that even rhythmic compression of the chest, which cannot possibly favor the entrance of air into the collapsed lungs, serves only to pump blood into an already damaged head and brain. The condemnation of all such methods is to be praised.

2. *Temperature Stimulation.*—The use of hot and cold water for stimulation of the skin is also a common practice. Cold water only serves to lower the general body temperature, and thus the general resistance of the child. We find that the majority

of newborn infants come from the delivery rooms with subnormal temperatures even under the best of conditions. Cold water as a stimulant is unphysiologic and should be as much condemned as body manipulation.

Immersion in warm water, on the other hand, while of no value from a stimulation sense, does preserve the child's body temperature, and hence, its resistance. It simulates intrauterine life and is helpful to the child's well-being.

3. *Removal of Foreign Material.*—This is one of the most important procedures of resuscitation. It must be remembered that before satisfactory respiration can occur, the air passages must be cleared. The aspiration of amniotic fluid, vernix caseosa, lanugo hairs, and epithelial cells furnish one of the most common causes of pneumonia. Farber and Sweet found amniotic sac contents in the lungs of 88 per cent of 124 infants. The obvious necessity of removing foreign material from the air passages before any type of stimulation is attempted needs special emphasis.

This, again, should be accomplished by simple means. A common, soft-nosed rubber catheter, size 12, can be used with safety in the mouth and nose. After birth the baby can be laid for a moment with the head lower than the body and the larynx, and trachea milked toward the mouth. The catheter is then resorted to, to clear out the nose, mouth and throat.

Especial emphasis should be laid on the use of soft catheters and not too vigorous manipulation, as damage may be done to the nose and soft palate. The practice of wiping out the infant's mouth with a piece of gauze is to be condemned as it only serves to injure the delicate mucous lining.

4. *Resuscitation With Air or Its Constituents.*—a. *Air:* This is one of the oldest means of combating asphyxia neonatorum and is particularly important because of its ease of administration. In its simplest form this consists of breathing into the mouth of the newborn infant. The use of other respiratory gases in the last few years has rather decreased the use of this simple method; also, there are two drawbacks to its use.

The first is the contamination of the mucosa of the air passages of the newborn with the breath of the resuscitator, particularly if he is suffering from a cold or is a carrier of bacteria. The second is the danger of rupture of the alveoli by too much air pressure. As to the first criticism, the practice of direct mouth-to-mouth breathing is certainly bad. This can be obviated, however, by placing several thicknesses of gauze between the mouth and nose of the newborn and the resuscitator, or by the use of a tracheal insufflator equipped with a stop bulb.

The problem of too much insufflation may be overemphasized. Since Standler, Davis and Stevens observed 1 per cent of spontaneous pneumothorax in 702 routine x-ray examinations of newborns, this may be more common than is ordinarily supposed. However, I have never seen a case of lung damage from mouth-to-mouth insufflation. There is no doubt that care should be used, and this applies to intratracheal insufflation as well. From 15 to 20 c.c. of air under a pressure of 15 to 20 mm. of mercury is sufficient to inflate the lungs of the newborn. Thus very little exhalation is needed to accomplish the desired pressure.

b. *Oxygen:* This has long been the standard treatment, and there is no argument against it. It is now so commonly used in combinations with carbon dioxide that they will be considered together.

c. *Carbon Dioxide:* Henderson, acting upon the knowledge that in the adult a partially asphyxiated respiratory center requires more carbon dioxide to stimulate it, advocated the administration of carbon dioxide to stimulate respiration in asphyxia neonatorum. McConnel and McCormac reported that in the use of oxygen alone for three years, there was no decrease in the mortality of asphyxia neonatorum, but that in using 5 to 25 per cent carbon dioxide in combination with oxygen, they found the mortality was greatly lessened.

At first, expensive inhalators were devised to dispense the carbon dioxide and oxygen in the correct proportions, but these are not essential, for tanks of the mixed gases may be purchased from any medical supply house. Two different proportions can be obtained; one with 5 per cent carbon dioxide and 95 per cent oxygen, and the other with 10 per cent carbon dioxide and 90 per cent oxygen.

The amount of carbon dioxide given varies from 5 per cent to 30 per cent. Henderson advocates 7 per cent. Boothby says that higher mixtures are dangerous. Those who use higher mixtures say that if the mixtures cause gasping or struggling, they should be stopped, not abruptly, but by gradual lowering. Nearly everyone advocates giving the mixtures at not longer than five- to ten-minute intervals several times a day.

While the efficacy of carbon dioxide stimulation is generally accepted, there are some dissenting ideas that have never been satisfactorily explained. Eastman has found that the carbon dioxide tension of the fetal blood is normally higher than that of the maternal arm vein. One must assume, therefore, that in utero the sensitivity of the fetal respiratory center is depressed by carbon dioxide. Furthermore, the primary blood change in asphyxia neonatorum is a reduction of the oxygen content of the blood to extremely low levels. The serum pH of an asphyxiated infant is reduced to unsupportable levels, sometimes below 7.00. This indicates that the use of carbon dioxide as a resuscitating agent in asphyxia neonatorum is not only superfluous, but may even be harmful. What the infant needs is oxygen or air.

I simply wish to show that perhaps it is the oxygen in the mixture that is the cause of the good results. Coryllos has shown that oxygen passes more easily from the air sacs to the blood when carbon dioxide is present. This may be another reason. Until these questions are settled, it would be wise to continue the use of 5 per cent carbon dioxide and 95 per cent oxygen mixture, but certainly not in a greater proportion. Personally, I have never observed any different effects from the added carbon dioxide than were observed with pure oxygen.

There is one exception to this—in infants suffering from morphine narcotization. Here the respiratory center is apparently depressed far below its normal function. Shute and Davis in 120 narcotized infants used carbon dioxide in 10 to 30 per cent mixtures with oxygen in thirty-six of these infants and had but two deaths; while of the eighty-four who were not so treated, eight died.

d. *Drinker Respirator:* Murphy and Sessions used this apparatus in 1922 with great success, and it has been used much since. They state that there were no injurious effects and that it was of value in all types of asphyxia neonatorum, particularly in premature infants. We have been using the Drinker respirator routinely for the past five years. We believe that it can be used in all types of asphyxia neonatorum except those due to cerebral hemorrhage. The reason for this is that in the respirator the head is lower than the body, and, until the infant accommodates himself to breathing, there is considerable crying and struggling. I think that all this must only aggravate the hemorrhage, and in any case the trouble is cerebral and not in lung aeration. Second, before respiration begins, any material occluding the upper air passages must be cleared out, as has before been stated. You cannot aerate the lungs until the air passages are clear, and there is a possibility of drawing the material down into the bronchi and air sacs.

Practically, we use only a negative pressure of 10 mm. of mercury. Murphy advocated a positive pressure as well in severe asphyxia, but we have never used it. The respirations are set for thirty per minute, and the child is never kept in the respirator for more than one hour at a time. Several hour treatments may be given during the day. In premature infants with recurrent cyanotic attacks, treatments may be given for several days. I have given them for as long as two weeks. There is some idea that the respirator may injure the child.

Murphy and Bauer, in thirty autopsies on infants who died after respiration, found that there was a slight increase in pulmonary congestion but that no cellular material was found in the air passages. They concluded that there was no evidence of injury and that in atelectatic conditions the pressure could be increased to 15 mm. of mercury.

The respirator has also been criticized because it fails to regulate the carbon dioxide content of the circulating blood. To me the clinical success of this method answers the criticism and further raises the argument as to the necessity of carbon dioxide.

I do not believe that any method has been satisfactorily devised to treat severe atelectasis, but the principle of the respirator is as good as any. It offers an instantaneous method for creating a satisfactory degree of pulmonary ventilation accurately.

The chief drawback to the Drinker respirator is its costliness, and this is a serious one. I do not think the respirator is particularly necessary outside of its ease in handling the infant. Certainly no one should feel that any particular infant who could not have been saved by other methods could have been saved by a respirator.

e. *Medical Stimulants:* Naturally all manner of cardiac and respiratory stimulants have been used, have had their vogue, and later have been discarded. Among these are digitalis preparations, adrenalin, and more recently, lobelin. The first two are of doubtful value. Certainly, in cerebral hemorrhage, they might be harmful by increasing the blood pressure and causing more hemorrhage. Lobelin is presumed to be a direct central respiratory stimulant. Its administration intramuscularly or by injection into the umbilical vein is a simple way to try and stimulate respiration. The drug is safe, except in large doses or in too frequent doses. Lee reports two deaths in infants from its use.

Bonar has summed up certain principles that should be applied as universal in the treatment of asphyxia neonatorum.

1. All measures of a violent nature should be prohibited.
2. Absolute rest, warmth, and quiet should be maintained.
3. The air passages should be cleared immediately.
4. Adequate fluid intake should be maintained.
5. Oxygen, or regulated doses of 5 per cent carbon dioxide and 95 per cent oxygen, should be administered.
6. In the absence of gases, extremely gentle intratracheal insufflation of air, or possibly mouth-to-mouth insufflation should be used.
7. The administration of lobelin in moderate doses should be tried.
8. Asphyxia, complicated by evidence of intracranial pressure, seems to justify immediate treatment, either by giving blood injections, removal of an adequate amount of cerebrospinal fluid, or both.
9. Recurring attacks of asphyxia should receive the same attention as immediate asphyxia.
10. Roentgenograms of the chest are of great value in determining the cause of the cyanosis.

DISCUSSION

CHAIRMAN PARMELEE.—You have heard Dr. Sanford's thorough discussion of the respiratory difficulties of the newborn with special reference to treatment. I should like to have all of you enter freely into the discussion of this important subject. If Seitz's statement that 3.5 per cent of all infants are born in a state of deep asphyxia is true, the subject is indeed important.

DR. R. N. ANDREWS (MANKATO, MINN.) asked whether the use of a tracheal catheter in resuscitation was considered dangerous. He reported the case of an

infant thus resuscitated who died after thirty-six hours; necropsy showed ruptured alveoli in addition to bronchopneumonia.

He also inquired about the value of dilating the anal sphincter as a means of stimulating respiratory activity.

DR. P. A. McLENDON (WASHINGTON, D. C.) described an apparatus used in Washington for resuscitation called the Christman apparatus, with which very good results have been obtained.

He spoke also of the danger of cramped position of the infant's head in interfering seriously with breathing. He advocated placing some sort of a pad under the shoulders of an infant having any respiratory difficulty and leaving the pad there until he is breathing normally.

DR. C. E. BRADLEY (TULSA, OKLA.) made a plea for better teamwork between obstetricians and pediatricians in the technic of resuscitation. He felt that the practice of tilting the bassinet so that the infant lies with his head lowered for the first hours of life is not physiologically sound and is more likely to do harm than good.

The frequency of intracranial injury as a cause of respiratory difficulties would seem an important reason for restricting manipulations to the minimum.

DR. I. R. COHN (TOLEDO, OHIO) spoke of the possibile rôle of sepsis in the etiology of atelectasis. He asked how infants with secondary atelectasis can be aided in the inflation of their lungs without the aid of a respirator.

DR. GEORGE R. MURPHY (ELMIRA, N. Y.) emphasized the importance of first clearing the air passages before using any type of respirator or resorting to other manipulations. He spoke favorably of the Flagg resuscitation apparatus. The urgent necessity of teamwork in obstetrical and pediatric departments was stressed.

DR. E. R. McCLUSKY (PITTSBURGH, PA.) spoke of his experience with a European respirator, a modification of the Drinker, but operated on the same principle. He spoke of his experience with an oxygen tent which is a modification of the Cecil-Blummer tent made to fit over a crib or a bed for a premature infant. In this, oxygen is kept at a concentration of about 50 per cent and set at that so it cannot be changed. One great advantage of this method is that the child can be put in it and left there for some time. Oxygen alone instead of a mixture of carbon dioxide and oxygen is being used more and more. It was his impression that they were getting better results with the oxygen-tent method than with the respirator.

DR. JAMES KRAMER (AKRON, OHIO) spoke of attacks of asphyxia occurring in the first days of life in babies with a cleft palate deformity, the tongue causing complete obstruction of the nasopharynx. He also referred to infants having attacks of coughing and cyanosis each time they were fed; seven cases of this sort had come under his observation, and all seven infants had finally died of bronchopneumonia; one of these infants lived a year.

DR. THURMAN B. GIVAN (BROOKLYN, N. Y.) described an inexpensive and satisfactory apparatus for administering oxygen to newborn infants.

DR. S. C. HENN (CHICAGO, ILL.) said that while it was important to keep infants with asphyxia from being chilled, it was wise to avoid overheating such as might occur in certain types of incubators. He spoke of the aid in diagnosis of the cause of respiratory difficulty that might be obtained from roentgenograms.

DR. DAVID J. LEVY (DETROIT, MICH.) spoke of cyanotic attacks occurring in the first days of life in infants having loud systolic cardiac murmurs which dis-

appeared within a week or so. Roentgenograms taken during the period of cyanosis and dyspnea showed great enlargement of the heart, and films taken after ten days showed a heart of normal size.

DR. A. LEVINSON (CHICAGO, ILL.) thought there was danger of confusion in our discussion when we spoke one moment of asphyxia, then of cyanosis, and then of atelectasis, while apparently talking about the same thing. He spoke of the difficulties encountered in making a clinical diagnosis of atelectasis even with the aid of roentgenograms.

Intermittent cyanosis he felt was usually due to intracranial hemorrhage, while continuous cyanosis is usually due to a heart condition. These two conditions are not always easily differentiated. In either case the child should be kept strictly quiet, not taken to breast, not bathed, not weighed or handled at all. The child is fed by a dropper and given oxygen.

The infant just born and in a state of asphyxia needs to be treated. He agreed with Dr. Sanford's methods of handling these cases but had not used the Drinker respirator because of fear of the damage it might do to the lungs.

Oxygen alone, he felt, was preferable to mixtures of oxygen and carbon dioxide, and he considered oxygen a very valuable aid in treatment.

DR. H. GORDON (BROOKLYN, N. Y.) advised caution in making a diagnosis of enlarged thymus as a cause of respiratory difficulty. Cyanosis is sometimes due to more obscure changes occurring in the process of transition from prenatal to postnatal conditions. Before birth the adrenal cortex is very large and has a good deal to do with tissue respiration. Upon the beginning of pulmonary respiration, there is immediately a change; the child must adopt himself to the new environment with the increase in oxygen tension and also in oxygen supply. As a result, in some instances infants show weakness and inability to adapt themselves. In such cases we find a good deal of cyanosis.

He also spoke of the danger of damage to the lung tissue in the use of the respirator.

DR. SANFORD said that in five years of use of the respirator no child at necropsy had showed any damage to the lungs. This may be because infants are never kept in longer than an hour at a time, no positive pressure apparatus is used, and negative pressure is never more than 10 mm. of water.

DR. S. H. ASHMAN (DAYTON, OHIO) cited the case of an infant born normally who at birth was cyanotic, had physical findings of atelectasis, and had also an asthmatic type of breathing. A roentgenogram showed moderate atelectasis and no evidence of thymic enlargement. At necropsy numerous thrombi were found in the lungs with diffuse bronchopneumonia which proved to be of streptococcic origin. This must have been a prenatal infection.

He spoke also of secondary atelectasis as a cause of cyanotic attacks that occur after the first days of the newborn period.

Pneumonia due to aspiration of amniotic fluid was discussed, and he felt it was more common than it is usually thought to be.

He cited a case of hemorrhage into the lateral cerebral ventricles which gave marked symptoms of respiratory difficulty. This case responded well to ventricular tapping.

DR. JOSEPH I. LINDE (NEW HAVEN, CONN.) emphasized the importance of aspiration of amniotic fluid or other material as a cause of cyanosis, especially in those cases in which the cyanosis comes on a few hours after birth.

He stressed the advantages of the tent method of administering oxygen and carbon dioxide over the mask method.

There followed a discussion of different types of oxygen tents, especially of the one being demonstrated by the makers of the Drinker respirator.

DR. MARTIN M. MALINER (BROOKLYN, N. Y.) asked if there was such a thing as delayed familial atelectasis. He cited the cases of three children in one family in which each had exhibited an almost identical clinical history: after normal births they had shown intermittent attacks of cyanosis during the first two days, then had recovered, but after two months they each had an attack of dyspnea with cyanosis and fever. The physical and roentgenographic findings were those of atelectasis on the right side. Recovery occurred, but periodically such attacks would recur with the same findings. These children are now five, eight and ten years old, respectively.

CHAIRMAN PARMELEE.—There is a condition called "congenital atelectasis," which gives exactly that clinical picture, but I know of no familial disorder of that sort.

DR. MAURICE L. RIPPS (ELIZABETH, N. J.) asked about the frequency of finding a patent ductus arteriosus associated with atelectasis also if concavity or angulation of the ribs was of value in diagnosing atelectasis.

He cited a case in which convulsions, crowing respirations, and spasmodic clenching of the hands might suggest spasmophilia, but he was of the opinion that cerebral hemorrhage was more likely the cause.

CHAIRMAN PARMELEE said that in his opinion every case of convulsions during the newborn period should be considered due to intracranial damage until definitely proved otherwise.

DR. CHARLES A WILSON (DETROIT, MICH.).—The ductus arteriosus is found to be patent in nearly all infants who die in the first week of life, and scattered areas of atelectasis are also usually found. It cannot be said that the atelectasis is related to the patent ductus. Areas of atelectasis are often found at necropsy in infants who have had intermittent attacks of cyanosis. It is very difficult to demonstrate these atelectatic areas in roentgenograms. Intracranial injury is found to be the cause of death in most of these cases. A large area of atelectasis that can be recognized roentgenologically may cause repeated attacks of cyanosis with recurrent attacks of fever over a period of years.

CHAIRMAN PARMELEE.—It is natural that there should be some confusion in the application of such terms as cyanosis, atelectasis, asphyxia, etc. Disturbances which occur in setting into motion the respiratory mechanism must almost certainly affect the circulatory apparatus which is so intimately related to it and is itself undergoing a profound rearrangement in these first days of life.

The meeting was adjourned.

FIRST ANNUAL CLINICAL MEETING OF REGION III OF THE AMERICAN ACADEMY OF PEDIATRICS

The annual conference of Region III of the American Academy of Pediatrics was held Oct. 4, 1934, at the Mayo Clinic, Rochester, Minn., and Oct. 5 and 6, 1934, at the University of Minnesota, Minneapolis.

The meeting was called to order by Dr. Henry Helmholz, chairman. Dr. B. W. Carey acted as secretary.

REPORTS OF STATE CHAIRMEN

Ohio (Dr. C. W. Burhans, Cleveland).—The progress made by the Ohio committee during the past few months has been mostly in little things. Valuable contacts have been made with child welfare organizations and Parent-Teacher Associations, and we have been asked to send a representative to their meetings.

Through the Ohio State Medical Association, we have cooperated in preparing diets for infants and children for use by the State Relief Commission.

The Bureau of Child Hygiene of the State Department of Health has been, because of financial reasons, without an active head for the past few years. What little work that was carried on was done largely by nurses. A civil service examination was given last spring, and on July 1, Dr. A. L. Van Horn was appointed as the director of this department. Dr. Van Horn has been at the Babies and Childrens Hospital in Cleveland for the past three years, and his appointment makes a very valuable contact between the Department of Health and the Ohio members of the Academy.

The postgraduate instruction in pediatrics to general practitioners has been progressing slowly. This is probably largely because of inertia on the part of the Ohio committee, and especially its chairman, and partly because in sounding out the sentiment of the physicians in the state, it has not been possible to discover a great deal of sentiment in favor of it.

A further discussion of this question will take place at the meeting of the Ohio State Medical Association.

Michigan (Dr. Bernard W. Carey, Detroit).—The report outlined the governmental activities for child welfare throughout the state as well as those of the volunteer agencies, pointing out the opportunity of Academy cooperation with existing programs.

The activity of Michigan members has been directed toward membership, and the development of a postgraduate course for general practitioners in cooperation with the University of Michigan, State Medical Society, and the Detroit Pediatric Society.

The office of the state chairman has circularized the pediatricians of the state by letter in the interest of the American Board of Pediatrics and the meeting of the pediatric section of the State Medical Society. A special meeting was held to arouse interest in attendance at the Cleveland session of the Academy.

Indiana (Dr. Oscar N. Torian, Indianapolis) reported definite steps had been taken to form a state pediatric society and that an advisory committee to the State Health Department had been created and was functioning satisfactorily. Participation was reported in thirteen district postgraduate courses throughout the state. Work was

under way in the immunization program against diphtheria, and plans were under way for further activity in postgraduate instruction, immunizations, and a tuberculosis survey. Increased effort for members was also noted for the next year's program.

Minnesota (Dr. E. J. Huenekens, Minneapolis) reported splendid cooperation with both University and State Medical Society. Speakers are furnished to county medical societies for postgraduate instruction, and to Parent-Teacher Associations. Effort is being made to bring preschool children into the doctor's office for examinations. Agreement was made to give twenty-minute talks on periodic examinations before local parent-teacher associations, and each cooperating P. T. A. agrees to have each member assume responsibility for visiting ten families in an endeavor to have the children brought to the family doctor's office for health examinations. The physician charges his regular fee for these examinations.

Wisconsin (Dr. Abraham B. Schwartz Milwaukee) reported that the Medical Emergency Relief Program was under the direction of the executive secretary of the State Medical Society, and that this program was working satisfactorily. The Academy program was one of active cooperation with the County Medical Society. One meeting of state members of the Academy was held during the year.

Illinois (Dr. Maurice L. Blatt, Chicago).—Paper was submitted.

Iowa (Dr. Lee F. Hill, Des Moines).—The activities of the Academy have been linked up very closely with the State Medical Society and the State Department of Health. There is a committee designated as the "Committee on Child Health and Protection" and also a State Pediatric Society. The Academy works in close cooperation with both the above groups. These committees cooperating have to date set in operation a plan whereby all health programs of the state are referred to a committee in the local county so that the medical profession of the county is in close contact with, if not in charge of, the programs put on by the lay groups. This has not worked 100 per cent but is functioning much more smoothly than any previous system attempted. Also, the committee has reviewed all of the literature sent out from the Bureau of Maternal and Child Hygiene. This has tended to improve the quality and cut down the quantity of such distribution. Another matter which we have been interested in is the consent slip used in school immunizations by means of which an attempt has been made to send as much of this to the private physician as possible.

The committee has functioned further in relation to the state programs, and during the last annual meeting we were given one-half day of the three-day session. This year we held pediatric sessions on two afternoons. By cooperation with the Speakers' Bureau considerable information has been carried to the laity and practitioners from a pediatric standpoint.

Kansas (Dr. Paul G. Carson, Wichita).—Because of the very active political opposition on the part of the State Medical Society, and the small and widely scattered membership, activities of the members of the Academy in Kansas have, so far, been limited to educational talks to such organizations as the P.T.A., private schools, and a few radio talks.

This fall in Wichita we have finally been able to divorce the matter of immunization against diphtheria from the school physician and authorities. It is now to be done by the various individual physicians at the nominal fee of one dollar except in the case of those definitely indigent who are regularly receiving help from the county or city, in which cases, the county or city physician having constant contact and authority attends to it.

We hope to widen this very small opening wedge as rapidly as possible and ally ourselves, for the purpose of education, with all the public and private welfare organizations as well as educational organizations; the chief idea is to inform the public properly on the modern conception of the prevention of disease, with especial attention to the matter of contagious and infectious diseases, and the matters pertaining to nutrition. We have also a 4a audiometer and are testing the hearing of all school children in Wichita.

Nebraska (Dr. Clyde N. Moore, Omaha) reports efforts along usual health lines, the most important accomplishment being the formation of a Health Advisory Committee cooperating with the State Health Department.

Colorado (Dr. F. P. Gengenbach, Denver).—Besides the general work in child welfare carried on by Colorado members of the Academy, the most recent activity has been in a survey of crippled children in the state.

South Dakota (G. E. Zimmermann, Sioux Falls) reported little activity due to lack of cooperation of the Department of Health.

Missouri (Dr. T. C. Hempelmann, St. Louis) had no report.

North Dakota (Dr. R. E. Pray, Fargo) had no report.

New Business.—Dr. Clifford G. Grulee, secretary-treasurer of the Academy reported that:

The 1935 annual meeting will be held at or near New York City on June 7 and 8, the Friday and Saturday preceding the annual meeting of the American Medical Association to be held at Atlantic City. An attempt to secure special rates for the Academy meeting on all railroads is being made.

Dr. Grulee reported briefly on the work of the various committees.

A question was raised as to the wisdom and desirability of holding the Academy's meeting near the time of the American Medical Association meeting. The thought was expressed that the length of time consumed by the two meetings was prohibitive and would react on attendance at the Pediatric Section of the American Medical Association. Three members spoke on the desirability of holding the meeting entirely distinct from the American Medical Association session. The question of passing a resolution to this effect for submission to the executive committee of the Academy was mentioned but no action taken.

The following officers of Region III were elected for 1935: chairman of clinical meeting, A. Graeme Mitchell, M.D., Cincinnati, Ohio; vice-chairman, Albert J. Bell, M.D., Cincinnati, Ohio; secretary and editor, Jacob V. Greenebaum, M.D., Cincinnati, Ohio.

Next year's clinical session will be held in St. Louis, Mo., in November. This will be a joint meeting with Region II at the time of the annual meeting of the Southern Medical Association.

A motion that a message of best wishes for a speedy convalescence to Dr. Bell, who is ill, was passed.

A motion that the thanks of the session be extended to the Mayo Foundation and the University of Minnesota for the courtesies extended during the meeting was passed.

At a luncheon meeting of state chairmen, it was decided to create a committee composed of the chairmen from Iowa, Indiana, Illinois, and Michigan, who would formulate a program for state activity. This program will be discussed at a meeting of state chairmen held during the annual meeting.

ABSTRACTS OF PAPERS PRESENTED OCTOBER 4 IN THE SESSIONS AT THE MAYO CLINIC

Intestinal Polyposis. Harry M. Weber, M.D., Rochester, Minn.

Adenomas or adenomatous polyps, the histologic types that are most frequently encountered, increase in frequency from the upper part of the intestinal tract downward. They may be single or multiple and scattered sparsely or densely throughout the intestine. "Polypoidosis" refers to that condition in which the entire mucosa seems to have been transformed into a villous, convoluted mass of adenomatous tissue.

When polypoid lesions occur in any part of the large intestine, the rectum and lower portion of the sigmoid flexure will be involved in about 95 per cent of instances. Therefore, digital and proctoscopic examination will discover the vast majority of these lesions. Roentgenologic examination of the colon will determine the extent of polypoid involvement and demonstrate the presence or absence of polypoid lesions in segments of the intestine, which are beyond the reach of the examining finger and of the proctoscope. Unless they are large, ordinary roentgenologic examination does not demonstrate polypoid lesions. A method especially useful for this purpose is briefly as follows:

After the intestine has been thoroughly cleansed of fecal material, gas, fluid, and secretion by catharsis and enemas, the opaque enema is given in the ordinary manner under roentgenoscopic control. The patient is then permitted and urged to evacuate this enema as quickly and as completely as possible so that only a thin coat of opaque material remains adherent to the mucosal surface of the intestine. Again, under roentgenoscopic control, the intestine is redistended with air or some other inert gas. Stereoscopic roentgenograms are then made. This technic provides what might be called a transparent media. The internal surface of the lumen of the intestine is brought out in bold relief, and the recognition of these polypoid excrescences becomes a relatively easy task provided the rather complicated technic has been carried out properly. Because it is complicated, however, the application of this method to young patients, who are unable to give the same degree of cooperation expected from adults, is often difficult. When satisfactory roentgenograms are obtained, the diagnosis of small nondeforming intraluminal lesions in the large intestine is second in precision and accuracy only to direct examination with the proctoscope, surgical exploration, or necropsy.

Eosinophilia (Case Report). Laura M. Fisher, M.D., Rochester, Minn.

The child showed enlargement of the liver and spleen.

Examination of the blood showed hyperleucocytosis and eosinophilia. The highest leucocyte count was 104,000 per cubic millimeter, with 81 per cent eosinophiles.

As the child's health improved, the number of leucocytes and eosinophiles decreased, the percentage of hemoglobin increased, the liver and the spleen gradually became impalpable, and the general condition of the child improved.

A number of cases, in which the values for the eosinophiles were as high as 95 per cent, have been reported. Biopsy was performed in some of these cases, and others came to necropsy. Some of the cases were diagnosed as myelogenous leucemia, Hodgkin's disease, and pernicious anemia, while others were classified as eosinophilia with hyperleucocytosis.

The condition, which has been described in the case history, does not correspond with the other cases, which have been reported in the literature. In view of the longevity of the patient, the progressive improvement, and the comparative well-being, even during the stage when the number of eosinophiles were high, no definite

diagnosis made, and the condition has therefore been classified as a chronic blood dyscrasia with hyperleucocytosis and eosinophilia.

Study of Organ Hypertrophy. Frank C. Mann, M.D., Rochester, Minn.

Partial or complete restoration of the amount of tissue lost by removal occurs in most, but not in all, of the organs of the body after partial removal. This restorative process has been called physiologic compensation. There is a considerable variation in the different organs in the amounts of tissue restored and in the rate at which restoration occurs. In our experiments, splenic tissue is not restored after partial removal. There is usually very little restoration of thyroid tissue after partial thyroidectomy. The most marked restoration has occurred in the liver, kidney, colon, and stomach.

Seventy per cent of the liver can be removed from a rat, and complete restoration of the amount of tissue loss will occur within six to eight weeks. One kidney can be removed from a rat, and eight to ten weeks later the remaining kidney will have increased in size almost enough to equal the renal tissue removed. Two-thirds of the colon of a dog can be removed, and a year and a half later the capacity of the remaining portion will almost equal that of the whole large intestine at the time of removal. All the stomach of a dog, except a small rim around the cardia, can be removed, and at the end of four years normal gastric capacity will have been restored.

The causes and mechanism producing restoration after partial removal are probably not the same for all organs although there are some common factors. It would appear that, while considerably less than half of the normal amount of the various organs is sufficient to maintain life, a more nearly normal amount is necessary to take care of the peak load of functional activity which may be placed upon them. There also appears to be one factor common to all organs undergoing physiologic compensation, namely, an increased blood flow to the organ involved.

Considerable data have been accumulated in support of the theory that restoration of an organ, after partial removal, is owing to a physiologic need for a larger functional capacity of that particular organ. All functions of an organ, however, are not of equal value in causing a restoration of an organ. Our experiments would indicate that the function of furnishing a portal pathway is the most important of the various functions of the liver in causing restoration of that organ to occur after partial removal. On the other hand, excretion of the nitrogenous products of the urine is the most important function of the kidney in causing compensatory hypertrophy to occur in that organ.

Rocky Mountain Spotted Fever. Robert S. McKean, M.D., Rochester, Minn.

There is evidence that the area in which Rocky Mountain spotted fever may occur is increasing, and because this disease has a rapid onset with headache, chill, fever, pains in the muscles and joints and subsequent muscular eruptions, it may simulate some of the exanthematous fevers. Two cases of Rocky Mountain spotted fever, which were observed at the Mayo Clinic during the past year, are reviewed. Both cases were treated expectantly, and uneventful recoveries ensued.

Disturbances of Function of the Thyroid Gland. Roger L. J. Kennedy, M.D., Rochester, Minn.

Disturbances in function of the thyroid gland of children are not especially uncommon. Both hyperfunction and hypofunction occur, but there appears to be

some misunderstanding over what constitutes examples of each. In children symptoms of exophthalmic goiter are quite similar to those in adults and are sufficiently striking to warrant a reasonably early diagnosis.

One hundred and fifty-seven cases of exophthalmic goiter among children admitted to the Mayo Clinic have been studied. During the period of time in which these were seen, no instance of any other type of hyperfunction of the thyroid gland in children was observed. It would appear, therefore, that the terms "hyperthyroidism" and "thyrotoxicosis" are not only unnecessary but even incorrect when applied to children, as they do not indicate accurately the condition present, namely, exophthalmic goiter. Thyroid tissue in cases in which resection of the thyroid gland was carried out in all but two cases showed diffuse parenchymatous hypertrophy, thus substantiating the clinical diagnosis of exophthalmic goiter.

Hypothyroidism

Insufficiency of thyroid secretion among children varies in its manifestations, depending on the stage of development of the individual at the time when deprivation begins.

Endemic Cretinism.—Endemic cretinism, rare in this country, is a condition in which deprivation begins even before intrauterine development starts. One or both parents lack sufficient thyroid secretion.

Athyrotic Cretinism.—Athyrotic cretinism is a condition in which the thyroid gland either fails to appear or fails to develop and in which the child, during intrauterine life, receives its supply of thyroid secretion from the mother. Such children begin to show the effects of a lack of thyroid substance from six to eight weeks after birth. Supplying such a child early and continuously with a potent thyroid preparation will result in practically normal growth and physical development, but will probably not result in normal mental development.

Infantile Myxedema.—Infantile myxedema is a condition in which deprivation of the thyroid secretion does not take place before the infant has undergone an appreciable development under the influence of adequate thyroid secretion.

Juvenile Myxedema.—Juvenile myxedema is a condition in which the lack of thyroid secretion is not marked before the child is two years of age. In these cases, recognition of the condition and proper treatment will usually restore the status of the individual to near normal, the result to be expected in treatment of adults who have myxedema.

Infantile Muscular Dystrophy. John J. Slavens, M.D., Rochester, Minn.

Case reports of two sisters present rather unusual conditions, which are almost identical, differing only in degree. The weakness and wasting are universal, excluding only the facial and bulbar muscles. In the case of the older child, the speech has been affected despite an absence of weakness of the muscles involved in the act. Mastication and deglutition have not been affected. All the reflexes are present, the sensorium is unchanged, and the mentality is normal. There appears to be a uniform wasting of muscle tissue with absence of fibrillary twitchings.

Muscular dystrophy usually begins between the second and seventh years and frequently reveals pseudohypertrophy. In the present cases, the weakness is uniform. The children lack the characteristic attitude and gait; the symptoms began at an earlier age and progressed much more rapidly than in muscular dystrophy. However, it is felt that the condition affecting these two sisters is one of infantile familial muscular dystrophy.

Crystalline Cortin. Edward C. Kendall, Ph.D., Rochester, Minn.

The amount of cortin in the suprarenal gland is equal to approximately 1 per cent of the epinephrine in the same weight of gland. The amount of epinephrine present averages somewhat less than 0.2 per cent of the wet weight of the gland. Thus, less than 0.002 per cent of the wet weight of the gland is cortin. The amount of cortin in both glands of a beef is about 0.5 mg. and the weight of cortin in a single gland is therefore approximately 0.25 mg.

We have found that, after complete suprarenalectomy, dogs can be maintained in normal condition in respect to body weight and all other criteria which can be applied. The daily requirement for each animal can be determined by administration of the solution. In each case a certain minimal amount must be given in order to maintain the animal.

A patient who had a severe case of Addison's disease was maintained for eighteen days by administration of about 10 mg. of crystalline cortin each day, without development of signs of insufficiency. Finally, a dog which was suprarenalectomized by Dr. Mann was given the crystalline hormone during the eight days following operation. The dog received no other form of medication and survived the operation and appeared to be entirely normal at the end of eight days. He was placed on a high salt diet and has lived for several months.

We have, furthermore, found that the cortin in crystalline form is quite insoluble in water; one part will dissolve in about 10,000 parts of water. There is present in the solution, however, a more soluble form of the hormone which will exert the same physiologic effect, and, as far as can be determined, the weight of material in soluble form is the same as the weight required in crystalline form. The exact relation between the two forms has not yet been established, but the essential groupings appear to be aldehyde and hydroxyl groups. There is no change in molecular weight when the hormone assumes the less soluble form.

The problem of the chemical nature of the suprarenal cortex has now been reduced to a concrete problem in organic chemistry. We may feel certain that in the near future the structure of the crystalline hormone will be established; after this has been accomplished, we shall be in a position to know whether or not this complex substance can be made synthetically.

Benzol Persulphide Dusting Powder to Relieve Itching. Samuel Amberg, M.D., and Louis A. Brunsting, M.D., Rochester, Minn.

A substitution of sulphur for oxygen in the molecule of benzol peroxide might be of value in some forms of cutaneous infections. After a consideration of benzol peroxide as a hydrogen peroxide in which the hydrogen atoms are replaced by benzol groups, benzol persulphide may be regarded as a similar substitution product of hydrogen persulphide; that is the reason for its name.

Benzol persulphide can give off sulphur which may be transformed to sulphureted hydrogen, of which 25 per cent of the weight of the persulphide can be formed. Sulphureted hydrogen is not a harmless substance. From the intact skin it does not seem to be absorbed, but from an injured skin it may be absorbed. In infants it is said that sulphur ointment for scabies has led to intoxications with sulphureted hydrogen, which did not result from inhalation. With the relatively small amounts of persulphide used, it is very unlikely that conditions of danger would be realized; nevertheless, such a danger cannot be disregarded entirely. The substance is insoluble in water but soluble in some organic solvents, particularly in carbon bisulphide and in sulphonated bitumen (ichthyol).

We compared the effects on poison ivy dermatitis of talcum, powdered benzoic acid, benzol peroxide and benzol persulphide, rubbing these substances lightly into the skin. Talcum was without effect, benzoic acid had a slight and rather transitory effect, and later became irritating, while benzol peroxide and benzol persulphide were equal in their activity. This activity consisted in allaying the severe itching for from four to six hours, making sleep possible. The dermatitis itself was apparently not influenced. For a few minutes after the application the itching was not relieved or became even worse; after five to fifteen minutes, it ceased.

In some cases the full strength powder was irritating. The powder should be very fine. In these cases, at the start, ointments cannot be used; in later stages the substance can be used as ointment. We may say in ointment form we prefer the peroxide, which has some bacteriostatic action, which persulphide has not.

On some cases of insect bites, the substance was also efficient, such as the bites of sand fleas and mosquitoes. It also proved of value in a few cases of pruritis of the anus or vulva. In such cases the rubbing in of the powder may prove irritating, particularly if it is too gritty or if too much is used so that it cakes. These difficulties may be avoided. It proved inefficient in eczema and extensive allergic conditions of the skin with itching.

Partial Obstruction Resulting From Ileitis. Donald L. Gillespie, M. D., Rochester, Minn.

This case is an instance of inflammation of the small intestine. A boy had been ill for three and a half months with abdominal pain, fever, and tarry stools and was progressively growing weaker.

An exploratory laparotomy showed ileitis with partial obstruction.

Neuronitis. Frederick P. Moersch, M.D., Rochester, Minn.

Neuronitis, which has been described under various headings, may affect children. The clinical history is fairly typical. The findings may vary somewhat as to their location and severity. The most characteristic symptoms are reviewed. The importance of examination of the spinal fluid is emphasized as these findings may aid in establishing a definite diagnosis.

Some Experimental and Therapeutic Applications of Artificially Induced Fever. Charles Sheard, Ph.D., Rochester, Minn.

Experimental Data.—In this paper are presented results obtained with relatively short electric waves (7.5 to 20 meters) produced by a General Electric radiotherm having an approximate output of 150 to 400 watts. The experimental data obtained with *systemic* applications of high frequency energy show that in the living animal (dog) muscle tissue is affected slightly more than is subcutaneous tissue; intraarticular temperature is affected more than is muscle tissue. The reaction of anesthetized animals to general body hyperthermia with this agent is quantitatively different from that of the unanesthetized animals. Temperature measurements on the tissues of dead animals have shown that bone is heated much more markedly than is muscle tissue and have indicated that the temperature changes produced by the electric field are strictly dependent on the position and composition of the various tissues. By the employment of *local* applications of the short wave electric field (through the use of small condenser plates), there has been demonstrated the importance, therapeutically considered, of the relationship between the heat developed in deep-lying and superficial tissues, respectively, as dependent on the distance at which the condenser plates are placed with respect to the surface of the tissues.

By suitable procedures it is possible to produce relatively high temperatures in a chosen region (such as the knee joint of a dog) by means of local applications of short wave energy of sufficient intensity. Furthermore, these temperatures may be produced in the deep (intraarticular) tissue of the region without the production of appreciable increases in the superficial (subcutaneous) tissues of the region. Local applications in selected types of clinical cases have proved beneficial.

Clinical Application.—The therapeutic applications were carried on with two types of artificial fever equipment: (a) Kettering-Simpson, employing humidified air heated over electric strip-heaters and circulated in the closed chamber, and (b) incandescent lamps (infra-red radiation) operated and controlled electrically to produce the necessary environmental temperature. The rectal temperature of the patient, using either method, is raised rather slowly but steadily to the rectal temperature desired. This temperature ranges from 103.5° F. to 107° F., depending on the type of disease under treatment. The desired rectal temperature is maintained as uniform as possible for five hours. Treatments are repeated when found desirable or necessary.

From the data presented, the conclusions are drawn that: 1. The conception that fever is a destructive process only is being supplanted by proof that fever is a protective and defensive mechanism. 2. The value of induced fever is being established, since the result obtained in the treatment of syphilis, gonococcal infections, and arthritis can be attributed largely to the production of fever. Whether the effects of radiothermy and other means of producing artificial fever are comparable in all respects is a moot question. 3. Artificially induced fever is apparently very beneficial in all types of Neisserian infection and has been demonstrated to achieve outstanding results in conditions of early neurosyphilis.

Treatment of Progressive Muscular Dystrophy With Glycine. Walter M. Boothby, M.D., Rochester, Minn.

We have had twenty-seven cases of progressive muscular dystrophy under treatment with glycine for between eight months and twenty-six months. This series includes examples of all the various types of the disease and the patients vary in age from two and a half to fifty years.

Unlike the marked improvement that we obtain in many cases of myasthenia gravis, in these cases of progressive muscular dystrophy we have only obtained a general improvement in health, decrease in fatigability, and possibly a decrease in the tendency to taking cold easily. We have not obtained any evidence of a definite recovery in the function of a muscle the ability of which to contract was markedly repaired. The general improvement of the patient and the decrease in fatigability, which allows the patient to be more active all day long, must be distinguished sharply from an actual improvement in the condition itself and the regaining of any muscle function which actually has been lost. We believe that glycine is valuable in progressive muscular dystrophy for two purposes: (1) to decrease the fatigability and thus permit the patient to do more throughout the day, and (2) to improve the general nutritional condition in the hope that this improvement will retard the advance of the disease. In those cases in which this can be accomplished, it is a great and real benefit. In explaining this possibility to the patient, it is necessary to avoid raising false hopes of curing the disease, or suggesting that muscle tissue, which actually has been destroyed, can be regenerated.

Planning the Ketogenic Diet. Mary A. Foley, Rochester, Minn.

The ketogenic diet must be planned to meet the individual need. The calories required for the daily intake may be calculated by means of the Boothby-Berkson nomogram (Chart 1).

Mayo Foundation Standards for age and sex
Males Age
Females Age
IV
Feet and inches
Centimeters
II Height
Per cent above or below basal
VI Food Factor
Daily food allowance : calories
VII Food Allowance
Basal daily heat production : calories
V Basal Requirements
Surface area : square meters (Dubois)
III S.A.
Pounds
Kilograms
I Weight
FOOD NOMOGRAM
Directions: The standards for age are printed on the back of the common method of expressing age as of the last birthday. To determine the desired calorie allowance, proceed as follows: (1) Locate the weight on Scale I by means of a pin stuck through the eraser of a lead pencil. (2) Place the edge of the ruler against the pin and swing the other end of ruler to the patient's height on Scale II. (3) Transfer the pin to the point where the ruler crosses Scale III which gives the surface area in sq. meters (this value need not be read). (4) Holding the ruler against pin on the surface area scale, swing the left hand end of the ruler to the patient's standard for age and sex given on Scale IV. (5) Transfer the pin to where the ruler next crosses Scale V which gives the basal heat production of the patient for 24 hours and represents the calories of food required by the fasting patient when resting in bed (basal calories). The calories necessary for activity bear a percentage relationship to those demanded for the resting condition. The number of calories above basal that will be needed when at work will need about 50 per cent more than his basal calories. When activity is restricted, as in the hospital, the extra calories necessary will range from 10 to 30 per cent of the basal calories. Therefore (6) estimate the per cent of calories above the basal and locate this point on Scale VI. With the ruler connect this point with the point located previously on Scale V, and where the ruler now crosses Scale VII read the amount of food calories to be provided by the diet.

Chart 1.

With this material as a working basis we make our daily menus. A ketogenic diet in itself is not very interesting, and it requires much ingenuity to make it palatable.

A day of starvation is helpful in some cases. The ketogenic diet must be followed strictly. There are no halfway measures.

Constipation is a factor which must be considered in the management of the patient who is receiving a ketogenic diet. Many of the cathartics ordinarily prescribed contain sugar in some form.

The change from the high carbohydrate and moderate fat diet to the low carbohydrate and high fat diet occasionally results in nausea, vague pains, and loss of weight and strength. If nausea persists, a small amount of orange or tomato juice is helpful. The loss of weight, which varies between 3 to 5 pounds, is the result of dehydration. Adjustments are made within a week or two and the weight, which has been lost, is regained.

The Use of Ketogenic Diet in Urinary Infections: Demonstration of Determination of Necessary Concentration of Beta-Oxybutyric Acid and pH of Urine. Arnold E. Osterberg, Ph.D., Rochester, Minn.

It is important in prescribing the ketogenic diet to know more accurately the pH value and the concentration of beta-oxybutyric acid in the urine. The knowledge of these two factors is essential in determining whether the diet is being assimilated and metabolized to produce a urine which will be bactericidal. Hence, it is of distinct advantage to the clinician to have at his disposal simple procedures by which he is able to know for certainty these factors.

We have adapted the Rothera test by which it is possible to determine within a few minutes whether or not the concentration of beta-oxybutyric acid is greater or less than 0.5 per cent.

By the use of this simple procedure the clinician is enabled to know in a few minutes and with a minimum amount of urine whether or not the ketogenic diet is efficient. For more accurate knowledge of the concentration of beta-oxybutyric acid that is being obtained, one should determine its concentration in several specimens of urine which have been collected at different intervals during the day. This is for the reason that the concentration of beta-oxybutyric acid varies with the length of time subsequent to the ingestion of the fatty meal. By the use of these tests we feel that the clinician should know accurately the effectiveness of this type of diet and whether or not the ratio of fat, carbohydrate, and protein should be varied to effect greater efficiency and that guesswork is removed from this type of therapy since one cannot expect bactericidal action to be present unless these standards have been met.

The Clinical Results of Ketogenic Diet Therapy. Henry F. Helmholz, M.D., Rochester, Minn.

The ketogenic diet has been used in thirty-seven cases in which the patients were suffering from urinary infections. In the use of the diet early in our experience, we were in doubt as to what were the conditions necessary to bring about a cure, and only after an experimental and clinical study did we come to the conclusion that two conditions are necessary in order that a urine may have a bactericidal action: first, that the pH of the urine must be 5.5 or below; and second, that the concentration of beta-oxybutyric acid must be 0.5 per cent or greater. If a pH of 5.5 or less and 0.5 per cent concentration of beta-oxybutyric acid are present, it is safe to say that the urine will act bactericidally on *Eschericha coli, Bacillus proteus, Aerobacter aerogenes,* salmonella, pseudomonas, *Streptococcus fecalis, Streptococcus hemolyticus, Staphylococcus albus,* and *Staphylococcus aureus.*

From our experience we find there are four conditions that may interfere with the success of the diet: (1) the functional incapacity of damaged kidneys to excrete a urine of low pH and high beta-oxybutyric content; (2) the inability of the individual to digest the amounts of fat fed with the result that large amounts of fat are found in the stool and necessary ketosis never is achieved; (3) the inability of the patient to take the amounts of fat necessary to produce adequate ketosis; and (4) the presence of stones in the urinary passages.

Contrary to the experience of others, in eight of the sixteen cases in which there was stasis, it was possible to sterilize the urine and the urine remained sterile after the treatment was discontinued. In a number of cases there was a return of the infection at a later date; this does not discredit the method but indicates that conditions were such that reinfection was likely to occur. Whenever possible, the cause of the stasis must be removed.

Reducing Diets in Children. Russell M. Wilder, M.D., Rochester, Minn.

It has been said that obesity in childhood always indicates an underlying endocrine abnormality. The dictum is based on the fact that children who are fat resemble in some respects the clinical picture that is frequently referred to as the Fröhlich syndrome. It is apparent, however, that this resemblance is a superficial one. These children are too young to have developed sexually. However, give them time to grow, and nearly all of them reveal normal genitals; reduce them by proper dieting and the last resemblance to the Fröhlich syndrome disappears.

It is often stated that the obese child is difficult to reduce. This has not been true in my experience. He loses fat readily if the intake of food is rigidly supervised and made less than the total expenditure of energy. A plan for reducing is described which is based on the procedure advocated by Strang, Evans, and McCluggage and which has proved very satisfactory in my hands. It involves limiting the calories in the food to about 550; providing adequate protein, with particular reference to protein of high biologic value; and supplying extra vitamins as concentrates together with extra calcium phosphate. The rate of loss of weight on this regimen will vary depending on the original weight of the individual. It is as rapid as is theoretically possible, however, and the patients usually feel perfectly well. Probably because they are actually not underfed in any particular except calories, the patients on this diet do not tend to break the diet by surreptitious eating. A successful reduction is thus usually accomplished.

Indications for Sympathectomy in Hirschsprung's Disease. Alfred W. Adson, M.D., Rochester, Minn.

The correction of Hirschsprung's disease is a neurosurgical problem of reestablishing normal peristaltic movements and regulated periods of defecation. The surgical attack on the sympathetic nerves of the colon, sigmoid, and the internal sphincter of the rectum has produced satisfactory results. It is apparent that the inhibitory muscular responses of the colon, and the contracting stimuli to the internal sphincter of the anus from the sympathetic outflow are more powerful than the motor responses of the musculature of the colon and the inhibitory responses to the internal sphincter of the anus, which come from the parasympathetic nerve supply. Defective parasympathetic innervation might produce a similar effect since the emptying stimuli would be less than the filling and retaining stimuli.

Surgical Indications and Preoperative Preparation.—Surgical intervention is not instituted in the mild cases of Hirschsprung's disease in which medical treatment is adequate, but if it becomes necessary for the patient to return to the hospital more

than two or three times for emptying of the colon and the employment of a still more rigid regimen, sympathectomy is indicated. The administration of acetycholine, which inhibits the activity of the sympathetic nervous system, has served as a preoperative test in selecting patients for sympathectomy.

Sympathectomy now includes a resection of both lumbar trunks with the second, third, and fourth lumbar ganglions, and a wide resection of the superior hypogastric plexus, the presacral nerve, situated on the promontory of the sacrum in the triangular space below the bifurcation of the abdominal aorta. This procedure is employed to include all of the sympathetic fibers from the lumbar chain; all of the intermesenteric fibers, descending into the pelvis below the inferior mesenteric artery; and those fibers, which rejoin the hypogastric plexus from the inferior mesenteric nerve in the mesocolon of the pelvis; thus, leaving only a small group of fasciculi, which have followed the inferior mesenteric artery and its branches to the lower part of the colon, and the internal sphincter of the anus.

Chronic Ulcerative Colitis Among Children. J. Arnold Bargen, M.D., Rochester, Minn.

Between 1929 and 1934, thirty-nine children who had chronic ulcerative colitis were observed at the Mayo Clinic. Seven of these children were twelve years old. The other thirty-two children were between two and fifteen years old. On the regimen outlined, twenty-one of these patients are today clinically well; two are free of symptoms and have not had any recurrence of the trouble; five are improved at least 50 per cent; five are under active treatment; two are no better; and four have died of perforation, hemorrhage, extensive thrombophlebitis, or liver abscesses.

Preoperative Roentgenization of Tumors of the Kidney. Arthur U. Desjardins, M.D., Rochester, Minn.

Among the tumors of the kidney the most common are adenocarcinoma, which frequently affects adults on the basis of an established simple adenoma; embryonal tumors of the kidney affecting adults, and embryonal tumors among children, or as Ewing calls them, embryonal myosarcomas.

The one renal tumor which is distinctly radiosensitive is the embryonal myosarcoma or mixed tumor, so common among children, and to which the name of Wilms is frequently attached. The radiosensitiveness of these tumors is almost as great as that of lymphosarcoma. Unfortunately, while the primary tumor can usually be made to retrogress substantially so that in some cases it may even seem to disappear as far as clinical examination goes, few such tumors have been cured permanently by irradiation or by any other method. For a number of years some of the cases encountered here at the Mayo Clinic had been treated with roentgen rays only, while others had been operated on and an attempt made to remove the tumor. Neither of these two methods has yielded satisfactory results as far as cure or prolonged improvement is concerned.

During the last year or two we have been trying a new method, and this is to treat such tumors with roentgen rays, and after a certain interval (three to eight weeks) to remove the residual tumors by surgical means. It is too soon to know whether this combined method will yield results sufficiently superior to the methods previously tried to make it stand out as a definite advance in therapeusis. On theoretical grounds the results should be better.

It is possible that the Coutard method may prove a distinctive advantage. However, inasmuch as these tumors affect children and often occur in very young children, the possibilities of the Coutard method will have to be considered with con-

siderable care and judgment with reference to each individual case because this method is one which should be applied only to cases in which the general condition of the patient is still good and in which the patients can tolerate daily exposure to the rays for a sufficient length of time to build up a very large total dose. Therefore, it should be reserved for cases in which the tumor is not too large and in which complications have not set in. Otherwise, I fear that, instead of yielding improved results, the method might prove a detriment, at least to a certain percentage of patients. Another point in connection with the Coutard method is that it cannot be repeated more than once, and this only after a rather long interval (three to six months). In other words, it is a method designed to bring about a cure and should be reserved for cases in which a cure is at least within the realm of possibility. In cases in which such a possibility is out of the question, the patient should not be subjected to the Coutard method but should be treated with a different technic and with the idea of bringing about maximal improvement and yet preserving the possibility of repeating the treatment later, if this should be necessary.

Application of New (Mayo Foundation) Standard for Basal Metabolic Rates in Children With Exophthalmic Goiter. **Roger L. J. Kennedy, M.D., Rochester, Minn.**

Over a period of time, data have been accumulating in the metabolism laboratory of the Mayo Clinic which have been employed by Boothby and his associates in the construction of a new standard for the determination of the basal metabolic rate. A sufficient number of children of the various age groups have been studied to supply data upon which a curve of metabolic rates has been constructed, which is thought to be more reliable than those previously constructed. The use of the new Mayo Foundation standard in determining the basal metabolic rates of children who had exophthalmic goiter has brought out some interesting facts.

One hundred and fifty-seven children who had exophthalmic goiter have been admitted to the clinic in the past twenty-five years. Determinations of the metabolic rates have been made on most of the children admitted with this disorder since 1917. Until very recently, the DuBois standard has been followed, but for purposes of comparison the rates have been calculated by both the DuBois and the Mayo Foundation standards. These calculations have been studied biometrically, and curves, which represent the percentage frequency, have been constructed to demonstrate the distribution of the rates as determined by each standard.

Those children with exophthalmic goiter, who received no iodine previous to admission, showed high basal metabolic rates as determined by either the DuBois or Mayo Foundation standards. In some cases in which a clinical diagnosis of exophthalmic goiter was made and in which pathologic examination, following operation, revealed a diffuse, parenchymatous hypertrophy of the thyroid gland, it was found that the basal metabolic rates were surprisingly low when the customary (DuBois) standard was followed. Calculated by the new standard, this group is eliminated or else is very small, indicating that in this respect the new standard reflects more dependably the rate characteristic of the disease. If the group is considered as a whole and the mean value for the basal metabolic rate is computed, it is found to be higher by the new standard than by the old standard. According to the new standard, the mean value in a group of seventy children was +41.9 as compared to a mean value of +33.9 for the same group by the DuBois standard.

In the second group, those who received some iodine previous to their admission to the clinic, the same fact is evident. The lowest basal metabolic rates were those

which were calculated according to the DuBois standard, and the mean value for the group was found to be lower, +26.0 by the DuBois formula as compared to a mean of +33.0 when the new standard was employed.

It is evident also, in this group of children, that the administration of iodine had a definite effect on lowering the basal metabolic rates. When the mean values for this group and the first group were compared, a decrease of nearly 9 per cent was found.

In the third group, those who received intensive iodine therapy, the same facts concerning a comparison of the two standards were plainly revealed. There was a tendency for the DuBois values to be lower than the Mayo Foundation values and a very definite difference in the mean values by the two methods. Not only has this study revealed comparable facts concerning the two standards but also the striking effect of the administration of iodine to children who have exophthalmic goiter has been demonstrated. The mean values for the basal metabolic rates of those who received iodine in adequate amounts were reduced from +41.9 to +21.4, a reduction of 20+ per cent.

Equally interesting, no doubt, will be a study of a good-sized group of children suffering from hypothyroidism and a group of children who have obesity of the constitutional type, as well as those who have obesity of types that have been ascribed to dysfunction of the various endocrine glands. It appears likely that such a study will result in some definite alteration of basic conceptions regarding these conditions.

Demonstration of New Scales. Samuel Amberg, M.D., Rochester, Minn.

The platform of the scales is replaced by a metal beam, which is high enough to allow the scoop to be suspended from it, thus insuring a stable equilibrium. A few short chains are attached to the scoop and to the suspension beam to prevent tipping from side to side and forward, while the nearness of the scoop to the suspension beam prevents tipping backward. The scoop is very readily accessible.

The Suprarenal Cortical Syndrome Resulting From Cortical Tumors. Waltman Walters, M.D., Rochester, Minn.

In the past two years, since the advent of active preparations of the suprarenal cortical hormone, eight patients presenting the suprarenal cortical syndrome have been operated on at the Mayo Clinic with one death from apparently accidental causes. Although considerable variation may be encountered, the syndrome is generally characterized by hirsutism, amenorrhea, hypertension and hyperglycemia, and by obesity of the face, trunk, and abdomen. Acneform eruptions, cutaneous infections, and osteoporosis have also been common symptoms. Surgical removal of the suprarenal cortical tumors was followed by rapid return to normal of previously abnormal physical metabolic conditions.

Of particular interest was one patient, aged nine years, who presented all of the characteristics of the lesion, with what was found to be an encapsulated tumor, measuring $6 \times 4 \times 2$ cm., which was removed from the left suprarenal gland Oct. 30, 1933. Her return to normal appearance and normal physiologic conditions has been striking. The case is so interesting that a complete résumé of the history is given.

Chronic Dyspnea and the Thymus in Infants and Young Children. Gordon B. New, M.D., Rochester, Minn.

A diagnosis of enlarged thymus should not be made without a laryngoscopic examination to exclude the possibility of some conditions which have been described as being the cause of chronic dyspnea, such as, congenital laryngeal stridor, bilateral

median line postoperative vocal cord paralysis, neoplasms, congenital subglottic diaphragm, lingual thyroid, and obstruction of the posterior nares. Enlarged thymus, with the exception of neoplasms of the thymus, can seldom be the cause of death, which results from respiratory obstruction. There has been no death attributed to hypertrophy of the thymus which has occurred during or after operation in infants and young children. No treatment has been given for enlarged thymus in any case.

Postoperative Thrombophlebitis of the Inferior Vena Cava. Charles E. Ward, M.D., Rochester, Minn.

A case of postoperative thrombophlebitis of the inferior vena cava in a child is reported because of the recovery of the patient and his almost complete compensation for the total occlusion of the main venous trunk.

Following an operation for removal of a gangrenous appendix on the ninth day of an otherwise uneventful convalescence, the left lower extremity became very painful, markedly swollen, and edematous. Pulmonary infarction was suspected on the twelfth day because of cough, and pain in the left axilla. On the fifteenth day the right lower extremity went through the same sequence of events previously noted in the left, thus indicating complete obstruction of the lower inferior vena cava.

The fever, swelling, and edema of the lower extremities gradually subsided in the course of eight weeks.

ABSTRACTS OF PAPERS PRESENTED OCTOBER 5 AND 6 IN THE SESSION AT THE UNIVERSITY OF MINNESOTA

Hepatonephromegalia Glycogenica—Glycogen Storage Disease of von Gierke. Robert L. Wilder, M.D., Minneapolis, Minn.

Enlargement of the liver and kidneys due to excessive storage of glycogen was first reported by von Gierke in 1929. Since that time, sixteen additional cases have been reported. Findings of the case reported show: that this is a case of glycogen storage disease; that the liver lacks ability to store excess intravenous saline; and that this disturbance may be due to hypophyseal or hypothalamic disturbance.

(To appear in full in the JOURNAL.)

Effect of High Sodium Chloride Ingestion on Blood Pressure and Carbohydrate Metabolism in Diabetic Children. Willis H. Thompson, M.D., and Irvine McQuarrie, M.D., Minneapolis, Minn.

In the course of a study of the factors involved in the abnormal craving for salt manifested by a severely diabetic boy, it was observed that the daily ingestion of between 60 and 80 grams of NaCl caused a marked elevation of blood pressure and a significant decrease in glycosuria. These observations were made repeatedly while the patient was maintained on a standard diet and received a uniform dosage of insulin gauged at such a level as to permit a moderate degree of glycosuria at all times. Ingestion of the extra salt for a period of a few days caused the systolic pressure to rise from an average level of 110 mm. of mercury to 175 mm. and the diastolic from 80 to 115. At the same time the urinary glucose excretion fell from between 60 and 70 grams to between 10 and 20 grams daily. Apparently this result was dependent in part upon the diets being relatively low in potassium.

That these phenomena were not peculiar to the patient who suffered from an abnormal craving for salt was shown by the fact that two other diabetic children

showed similar though less marked reactions under the same conditions except for somewhat lower salt intake. In one experiment in which KCl was substituted for NaCl the blood pressure was lowered while the degree of glycosuria was increased.

Several phases of the problem are being further investigated.

Hypoplasia of Enamel of Teeth (Familial). Lawrence F. Richdorf, M.D., Minneapolis, Minn.

Cockayne has described hypoplasia of the enamel of the teeth, or agenesia of the enamel. The condition affects both the teeth of the first and second dentition. The teeth are often brown when erupted and are not as resistant as teeth with normal enamel. In every instance affected members pass on the anomaly to the next generation. Not all are affected, the proportion in the known cases reported and summarized by Cockayne being 86 affected to 51 not affected. The number of males to females affected were 47 to 48, respectively; the proportion of normal males to females 24 to 22. The defect is a dominant, with no limitation to sex and with a greater occurrence of the abnormal.

The family to be reported is of interest because of the extensive enamel lesions and the recurrence of the same for five generations. Two other families have been found but this is the first time opportunity for study has been afforded.

Factors Responsible for Involuntary Defecation in Children. Hyman S. Lippman, M.D., St. Paul, Minn.

There are physical as well as psychologic factors responsible for the child's soiling himself at an age when this should no longer occur.

One case was that of a young child who failed to be trained because of the marked anxiety displayed by the parents that she be trained. When the parents were made to understand that it was their anxiety that was causing the sphincter spasm, their attitude changed and the problem cleared up.

Occasionally a child placed in a boarding home against his wish may soil himself, hoping that through this behavior he will become unbearable to the boarding mother and will be returned to his own home. In such instances the habit ceases as soon as the motive is recognized, and the child is helped to accept the situation from which he is trying to escape. It is frequently impossible to determine to what extent the soiling is due to willful behavior and how much of it is due to factors over which the child has no control. Intensive interviewing may be necessary to establish this point.

We have been able to understand more clearly the part played by anxiety of a subtle nature in the production of involuntary defecation through the contributions of the psychoanalytic school. Analysis of young children has demonstrated that the disgust shown toward the stool is a reaction against a forbidden pleasure; that the young child fights to retain the power to decide when and where he shall have a bowel movement; and that peculiar character traits are associated with an exaggerated interest in stool.

Congenital Megacolon Treated by Daily Hot Irrigations of Normal Saline at 115° F. Aaron Friedell, M.D., Minneapolis, Minn.

Hot saline irrigations at 115° F. are recommended as worthy of further investigations in treating megacolon. Irrigations to be given slowly and overdistention to be avoided. The film shows a method of procedure and the apparatus used to make the daily irrigations simple.

Significance of Hyperventilation in the Tetany Syndrome in the Newborn. W. Ray Shannon, M.D., St. Paul, Minn.

This case is offered as clinical evidence supporting my recent theory that such primary pathologic states as asphyxia, cerebral injury, atelectasis, etc., may give rise to the tetany syndrome through the successive stages of anoxemia, hyperventilation, alkalosis (?), and a lowered ionic calcium. Cyanotic spells, such as occurred four hours after delivery in this case, are interpreted as hyperventilation phenomena and the nervous picture as due in the main to tetany and an accompanying cerebral edema.

Epidural Abscess. Emanuel S. Lippman, M.D., Minneapolis, Minn.

Dandy in 1926 first called attention to that epidural spinal abscess in a definite clinical entity. At that time he showed that it could be differentiated from other conditions which had a similar clinical picture, and he especially emphasized the importance of immediate surgery.

According to literature the pathology found was: 1. The abscesses are all in the spinal epidural space. 2. They are usually found in the thoracic portion of the space.

According to Dandy, these infections are due to: (1) extension from a neighboring focus of infection, namely, boils or anthrax in the nape of the neck, extrapleural suppuration, osteomyelitis of a rib or of a vertebra; (2) metastatic infection from a distant source; (3) a group with no primary focus (idiopathic); (4) an organism, usually the *Staphylococcus aureus.*

According to Dandy, there should be little if any difficulty in arriving at a diagnosis of an epidural abscess when the signs of spinal cord compression accompanied by fever and leucocytosis develop and the level of the spinal cord involvement is contiguous with a preexisting infection. If there has been no such previous infection, diagnosis should be made by the following symptoms:

(1) A terrific, almost unbearable and unrelenting pain in the back, or along the course of the spinal nerves or in the legs; (2) a latent period of from four to nine days between the time of onset of the excruciating pain, and the motor, sensory, and sphincter paralysis. In every instance paraplegia, as well as sensory and sphincter loss, have either been sudden or have become complete within forty-eight hours after its onset. In nearly all the cases reported, there has been a sharply defined bilateral loss of sensation which may ascend depending upon whether or not the epidural abscess has extended upward or has remained localized. In addition to this characteristic story, there is always high fever, tachycardia, leucocytosis, and usually tenderness and rigidity over the spine. The spinal fluid shows a somewhat increased cell count, usually of polymorphonuclears; and a complete block always exists in the spinal canal, hence low pressure.

The sudden onset of paraplegia usually leads to the diagnosis of myelitis or even thrombosis or embolism. These conditions may be eliminated (1) because of presence of the excruciating pain which for several days precedes the paralysis, (2) because of the tenderness and rigidity of the spine, and (3) by a demonstration of a spinal subarachnoid block.

Although meningitis might be diagnosed because of the rigid neck, positive Kernig sign, fever, and leucocytosis, yet the sensory and motor involvement and the absence of meningitic fluid, plus the presence of a spinal subarachnoid block, should easily exclude meningitis.

Inflammatory epidural tumors may cause similar pain, but they lack the characteristic sharp onset, are less fulminating, and are prolonged over a period of weeks or months instead of days.

Poliomyelitis does not have excruciating pain with localizations in the back, nor would it present a complete arachnoidal block.

The case which I should like to present is that of a thirteen-year-old girl admitted to the Minneapolis General Hospital, Dec. 10, 1933, complaining of urinary retention for thirty-six hours, severe excruciating pain in the back for ten days, and paralysis of the lower extremities one day.

The pain in the back just above the waistline at first was rather mild and was helped by hot water bottles; but during the last six days it had been very severe and no treatment relieved it. There had been some weakness of the lower extremities during the preceding four days with progressive difficulty in walking, the legs becoming numb, and in the preceding twenty-four hours, a complete paralysis of the lower extremities had obtained.

There was nothing in her past history or family history which had any bearing on the present condition.

On admission the patient weighed 86 pounds, and the temperature was 100.8° F. There was a complete motor and sensory paralysis below the thoracic vertebrae, mild neck rigidity, negative Brudzinski sign, absent knee jerks, positive plantar reflexes, and absent abdominal reflexes. The patient was quite alert mentally but complained continually of pain in the back.

Patient was catheterized and yielded a negative urine; blood count was 14,000 polymorphonuclears, otherwise negative. X-ray examination of chest and the thoracic and lumbar spines revealed no pathology. Diagnosis on admission was reserved. Spinal puncture a day after admission revealed pressure of 140 mm., clear fluid, cell count of 66 of which 50 per cent were polymorphonuclear leucocytes.

On the second day the level of anesthesia had risen to the nipple line. This line was sharply demarcated posteriorly at the fifth dorsal nerve on the right side, and on the fourth dorsal nerve on the left. There was moderate hyperesthesia above these levels.

Spinal puncture on the third day revealed the same as the previous one. Patient began to complain of weakness of arms, held them rigid, and toward evening had complete paralysis of upper extremities. Throughout this period in the hospital the patient complained continuously of the severe pain in back.

On the fourth hospital day a laminectomy was done. Our preoperative diagnosis was spinal cord abscess. The spines of the third to fifth vertebrae were removed. At the level of the fourth, much thick grayish green pus oozed out into the wound from the epidural space. Drains were inserted; patient returned to bed but died several hours later.

Autopsy was entirely negative excepting for findings at site of operation, which showed a large abscess extending from the third to the fifth thoracic segment with softening of the cord to almost liquefaction.

I have presented this case especially to emphasize the fact that because of failure of recognition, we delayed treatment of a condition which is almost as much an emergency as an intussusception.

Pediatric Aspects of the Cleft Palate Problem. Alexander Stewart, M.D., St. Paul, Minn.

The pediatric care of 251 children who have had over 500 operations for congenital clefts of lip and palate at the Children's Hospital of St. Paul is reported. In this group there were no deaths.

The cleft lips were repaired as soon as possible, most of them in the second month. Different complicated rubber dams and other apparatus designed for the feeding in cleft palate cases had been tried but were discarded for the Breck feeder which was found to be the most satisfactory method for mothers and nurses.

The feedings were of breast milk if possible. If a formula was used, it was more concentrated than in the case with the normal child. The greatest difficulty was the amount of air swallowed with the food; this problem required a lot of time and patience on the part of the mother.

A child was considered fit for operation: (1) when the gain was satisfactory; (2) when temperature was normal for twenty-four hours; (3) when there was no nasal infection; (4) when hemoglobin was about 70; (5) when leucocyte count and bleeding and coagulation time were within normal limits.

No routine x-ray picture of the thymus was made unless there were symptoms which indicated an enlarged thymus. Food was given to babies with cleft lips until six hours before operation. No sedatives given in cases of cleft lip. The cleft palates were repaired when the babies were fourteen months to two years old.

For the last two years we have been repairing the palate in two stages, first the hard palate and in about three months the soft palate. This has eliminated most of the severe reactions and rhinitis with pulling out of the sutures we formerly had when the repair was done in one operation.

Generally we do not give any preoperative sedative, but in the older children we have been trying moderate doses of sodium amytal. This seems to allay their fears and anxiety and keeps them quieter after operation.

Patients with cleft lips are given sterile water as soon as they can swallow and regular feedings in twenty-four hours. The cleft palate patients are given sterile fluids in eight hours; the food is sterile until the sutures are removed.

We found the Breck feeder with a rubber tubing attached more satisfactory than the dropper.

The building up of patients who are poor surgical risks and the postoperative care is a tedious and exacting type of nursing. The results depend probably as much on the nursing as it does on the surgeon.

Morquio's Disease. George K. Hagaman, M.D., St. Paul, Minn.

In the last few years there has been reported a growing number of cases of widespread osseous deformities, evidently produced by some interference with the transformation of cartilage into bone, as in chondrodystrophy, but not confined to the long bones and lacking the symmetry of that condition.

The case report of a child with the x-ray findings, especially in the upper extremity and in the spine, as well as in the acetabula, is similar to those described in the reports of Morquio's disease.

Undescended Scapula (Sprengel's Deformity—Congenital Elevation of the Scapula). J. Martin Sansby, M.D., and Leo G. Rigler, M.D., Minneapolis, Minn.

Two cases of deformity of the scapula and cervical region were presented, one in a child aged six years and the other in a child of eighteen months. In the first case the deformity, which is bilateral, was recognized when the child was ten days old. The other, first seen at six months of age, presents a right-sided deformity.

That the term "congenital elevation of the scapula" is not the proper designation for this deformity is evident when one considers the embryology of the scapula. In the light of our present knowledge, this condition should be known as "un-

descended scapula.'' It is often associated with other congenital deformities, such as defective ribs, numerical variations of the vertebrae, and spinal and muscular defect.

For practical purposes, this deformity may be divided into three types: (1) in which there is a defect in the cervical spine—usually spina bifida (an omovertebral bone may or may not be present); (2) in which there are muscle defects; (3) in which there is a bony bridge connecting the scapula to the spine with no spinal defects. In all the above types, as a result of the molding effects of the muscles, there is a forward bending of the supraspinous portion of the scapula.

Treatment varies with the character of the case. In cases in which the deformity is slight and the descent is not prevented by fibrous and bony attachments, gymnastics, passive motion, and stretching are all the treatment required. In cases in which the elevation is pronounced with marked deformity and in which articulations and adhesions are present, surgery is indicated. In all cases the after-treatment should be active exercise, passive motion, and massage.

The Cardio-Amplifier and Sound Tracings in the Diagnosis of Cardiac Murmurs. Paul F. Dwan, M.D., Minneapolis, Minn.

Four cases are presented with demonstration on the cardio-amplifier and accompanying sound tracings. The first is a normal heart; the next two are cases of mitral regurgitation; and the last a case of patent ductus arteriosis. The mitral cases showed the differences in tracing between a soft systolic murmur and a loud, harsh murmur. The last showed the harsh, prolonged, machinery-like murmur of patent ductus arteriosis.

Primary Sarcoma of the Suprarenal With Metastasis to the Skull. Charles L. Steinberg, M.D., St. Paul, Minn.

This syndrome, which is sometimes termed ''Hutchison's sarcoma,'' occurs in infancy and early childhood. Clinically it presents a picture so strikingly bizarre and grotesque that once seen it can hardly be forgotten.

The primary lesion is in the suprarenal gland, but the earliest clinical sign commonly observed is an ecchymosis of one or both of the eyelids. Within a very few days exophthalmus develops; this is usually unilateral. As this exophthalmus increases, a tumor mass or masses in the adjacent temporal and frontal bones appear, followed rapidly by metastatic enlargement of the preauricular and cervical lymph nodes. In some cases exophthalmus of the other eye occurs. Localizations elsewhere in the skull usually appear; sometimes metastatic growths in the ribs, vertebrae, and long bones are found. Peculiarly, the primary growth in the adrenal was found clinically in only about half the reported cases, and in these usually after the skull changes were manifest.

The metastatic tumor masses increase rapidly in size and number; at first they are rather firm and solid in nature, but commonly central softening of the masses occurs, producing a rubberlike consistency. These deforming tumor localizations in the skull produce a striking similarity of appearance of all of these patients.

A rapid spread of the malignancy is associated with a profound secondary anemia and progressive exhaustion. The leucocytic blood picture shows no definite changes. The entire progress of the disease is extremely rapid; death occurs in from one to six months after the initial ecchymosis is observed.

The postmortem findings are rather constant. The primary adrenal tumor varies from the size of a walnut to that of a cocoanut. It is usually unilateral. The adjacent kidney may be involved by extension, but the other abdominal viscera are

spared. The most extensive metastases are found in the calvarium and in the base of the skull, but the dura and brain are not involved. Occasionally, metastatic growths occur in the ribs, vertebrae, and long bones.

Microscopically, the tumor masses are composed of small round cells with very little stroma. In some areas these cells are arranged in rosette formations, characterizing this malignancy as a neuroblastoma as differentiated from the usual round cell sarcoma.

The clinical picture is closely simulated by chloroma which usually begins as an orbital tumor with subsequent multiple growths of the skull. Differentiation may be made by the leucemia-like blood picture and the more extensive and heterotopic metastases present in the latter disease.

Primary Peritonitis. E. J. Huenekens, M.D., Minneapolis, Minn.

A report of six cases of primary peritonitis, not including static peritonitis of infancy or the terminal peritonitis of tubular nephritis. The majority of cases are probably secondary to acute upper respiratory infections rather than ascending infections through the female genitourinary tract. The salient features which distinguish it from peritonitis secondary to ruptured appendix are:

1. Sex, 90 per cent of the cases occur in females.
2. It is frequently preceded by acute pharyngitis.
3. Severe symptoms develop more rapidly; the patients may be very toxic within twenty-four hours after the onset; the picture resembling a severe typhoid fever with abdominal symptoms.
4. The fever is high very early—103° to 106° F., and the white blood count ranges from 20,000 to 40,000.
5. It is nearly always accompanied by severe diarrhea.

The treatment consists of avoiding operation until the pus is localized, which may be two to three weeks after the onset. Although the Germans call this condition "pneumococcio Peritonitis," it is never preceded by pneumonia, but pneumonia and empyema are a frequent complication.

Although the available statistics vary greatly, it may be said that the prognosis is not good under any form of treatment, but is considerably better when early operation is avoided.

Recurrent Poliomyelitis. F. G. Hedenstrom, M.D., St. Paul, Minn.

Eleven cases of recurrent poliomyelitis are reported in the literature. The Gillette State Hospital has three additional cases to add to this group.

Apparently reinfections of poliomyelitis may occur although they are very rare. The reinfections may be explained on the same basis as other specific infectious diseases: (1) there is a complete lack of immune bodies or (2) the initial immunity is insufficient to protect against a second attack.

Lipiodol in the Diagnosis and Treatment of Chronic or Recurrent Parotitis. Tobias L. Birnberg, M.D., St. Paul, Minn.

Two cases of chronic parotitis are presented, chiefly to demonstrate the use of lipiodol in the diagnosis, and perhaps its value in the treatment, of this condition.

Periodic parotid swelling is of two types: (1) infectious, (2) noninfectious, due to stone, duct stenosis, or duct spasm. These types are differentiated by examining the expressed saliva; in the noninfectious type there are no cells and very few organisms.

The onset may be sudden or insidious, often after an acid meal. In the acute state the gland is hot, painful, and tender. There is slight fever. A ropy discharge, sometimes offensive in taste, may be expressed from the duct. Attacks last one to three weeks.

The cause may be: (1) local; as dental caries, tonsillitis, sinusitis, or stomatitis; (2) subsequent to an acute suppurative parotitis that has drained externally; (3) stone; (4) stenosis of duct; (5) tuberculosis, syphilis, or actinomycosis.

The involvement may be lobar, lobular, or diffuse.

The treatment consists of the following procedures: (1) massage of the parotid every morning before breakfast; (2) frequent gum chewing to stimulate the flow of saliva; (3) a glass of sour lemonade after meals; (4) treatment of local disturbances, as infected tonsils, sinusitis, or stomatitis; (5) improvement of general health and immunity by high vitamin diet and perhaps vaccine; (6) the use of lipiodol as a diagnostic and perhaps therapeutic aid. Its therapeutic action may be (a) similar to that of bismuth paste in the healing of chronic cavities or sinuses; (b) as an aid to drainage by dilating the finer ducts; and (c) its possible antiseptic action as suggested by some in pulmonary bronchiectasis; and (7) surgery, as removal of calculi or dilatation of ducts.

Prolonged Fever Following Encephalitis. Thomas Myers, M.D., St. Paul, Minn.

A female infant was presented with a complaint of almost constant fever following acute encephalitis ten months before. The condition is considered one of "cerebral" or "neurogenic" fever, due to a disturbance of the thermoregulatory center in the optic thalamus, resulting from acute encephalitis ten months previous.

The Liabilities Versus the Assets Originating From Primary Tuberculous Infections. C. A. Stewart, M.D., Minneapolis, Minn.

Wallgren has shown tuberculous meningitis to be an immediate hazard created by the first invasion of the body with the tubercle bacillus, and personal experiences combined with circumstances relating to the age at the time of death, identify miliary tuberculosis as a second immediate hazard attending primary tuberculous infections. The number of children who die annually with these two conditions following shortly after the first infection is laid down represents a heavy sacrifice paid for an alleged immunity.

The records of 11,400 children examined at Lymanhurst during the past twelve years identify phthisis as a remote liability created by the first infection with *Mycobacterium tuberculosis*. This statement is based on the fact that during this follow-up period more examples of this form of tuberculosis have arisen in the patients who entered Lymanhurst with positive tuberculin tests than in the group who were negative to tuberculin when first examined. The liabilities attending the initial invasion of the body with the tubercle bacillus include miliary tuberculosis, tuberculous meningitis and phthisis.

To date the Lymanhurst studies have disclosed no assets which can be attributed to the acquisition of tuberculosis of the first infection type. Apparently, therefore, the rather generally accepted belief that the first infection with the tubercle bacillus produces a beneficial protective immunity must be abandoned.

Natural Hypersensitiveness in Children. Albert V. Stoesser, M.D., St. Paul, Minn.

From 2,771 admissions to the General Pediatric Out-Patient service of the University of Minnesota Hospitals over a two-year period, 141 children, or 5 per cent, were referred for study and treatment to the pediatric allergic clinic. The cases

were distributed as follows: eczema, 43 (30.5 per cent); allergic coryza, 10 (7.1 per cent); hay fever, 19 (13.5 per cent); asthmatic bronchitis, 5 (3.5 per cent); bronchial asthma, 46 (32.6 per cent); urticaria, 15 (10.7 per cent); and gastrointestinal allergy, 3 (2.1 per cent). All of these cases can be classed under that subheading of allergy called "natural" or "human hypersensitiveness," which includes all clinical forms of allergy which occur so far as is known only in human beings and which are subject almost entirely to inheritance.

A Study of the Mortality of Premature Infants Delivered by Cesarean Section. Edwin F. Robb, M.D., Minneapolis, Minn.

A study of the mortality for premature infants delivered at the University of Minnesota Hospital and at Abbott Hospital for the past five years revealed a 41 per cent mortality for premature infants delivered by cesarean section and a 34 per cent mortality for premature infants delivered by vaginal methods.

The theory is suggested that a lowered blood volume may play a large part in causing the high mortality for prematures delivered by the present technic of cesarean section. With the present technic, whereby the cord is cut immediately upon opening the uterus, it would seem that a substantial amount of fetal blood in the placenta was lost to the baby. While the placenta is smaller in the case of a premature infant and no doubt contains less than 90 c.c. of blood, the percentage of blood lost in this way is high when considered against the small total volume normally present. It may in some cases represent as much as 33 per cent of the total blood volume. Any such percentage loss could account for many of the unexplained cyanotic attacks and fatalities that occur during the first forty-eight hours of life.

R. T. LaVake suggests that the present technic of cesarean section could possibly be modified, delivering the baby, cord, and placenta intact. If this were done, ample time could be allowed in clamping the cord. By thoracic aspiration on the baby's part and by mechanical pressure upon the placenta, much of the fetal blood present in the placenta might be obtained by the baby.

Furthermore, this same theory may apply to premature infants delivered by vaginal methods if the cord is cut before pulsation ceases. Delivery rooms should be supplied with suitable heat lamps and warm cotton gowns to protect the premature baby until all pulsation of the cord has ceased.

The Conservative Treatment of Late Cases of Acute Appendicitis. Owen H. Wangensteen, M.D., Minneapolis, Minn.

If every patient with acute suppurative appendicitis were operated upon early, there would be no necessity for this discussion. Procrastination, purgation, and perforation are the alliterative sequence synonymous with peritonitis and peril of the patient with acute appendicitis. The time interval following the acute attack, after which the nonoperative plan is to be preferred to operation is difficult to establish arbitrarily. It is the status of the patient rather than the time interval that is significant. If it is believed on the basis of the patient's reaction, viz., the pulse and temperature and the local physical findings, that the appendix is ruptured, it is wise to follow the conservative plan of treatment.

Speech Defects in Children. Bryng Bryngelson, Ph.D., Minneapolis, Minn.

The usual classification of disorders of speech is defective voice, articulatory deficiency, aphasia, and stuttering.

We think of good speech in children as being indicative of growth or maturation. Likewise inadequate speech is often indicative of a retarded growth of the nervous

mechanism responsible for speech. Disorders of voice and articulation can be caused by various obstructions in the peripheral speech mechanism. Hypertrophied tonsils and adenoids, nasal polyps, a too large or a too small tongue, malformed dental arches, short velum, inadequate frenum, deviated septum, and cleft lip and palate are the most common types of obstructions to free and easy articulation.

Many children have deficient hearing mechanisms. Certain frequency bands for specific sound groups may be missing in the child's audition. Defective "f," "s," "th," and "k" sounds are frequently due to the fact that those sounds have never been registered in the auditory pattern of the child even though they have been in the child's speech environment.

At present there are two main approaches to the problem of stuttering. Dr. Kopp at the University of Wisconsin is making a biochemical approach to stuttering. His metabolic studies have revealed that the blood pattern as shown by the correlations of total serum calcium, inorganic phosphate, total protein, and nonprotein nitrogen is practically the reverse of the pattern of nonstutterers. Some day it may be possible to assist stuttering therapy with certain diets.

At our own university we have been engaged in the approach known as cerebral dominance for the past eight years. By cerebral dominance we mean that in the act of speaking, one cerebral hemisphere, because of its greater strength, superimposes on the other hemisphere, its inherent rhythm, pattern, and intensity. Thus when the nerve impulses arrive on the bilateral midline speech structures, they do so simultaneously with similar pattern and intensity. Speech, then, becomes a concerted act sponsored by a very high type of integration of the central nervous system. In stuttering the power becomes equalized in both hemispheres, thus causing a reduction of cortical control over the substructures. A stutterer, it is indicated from Dr. Travis' experimental action current studies, does not possess a sufficiently strong gradient for speech resident in one cerebral hemisphere.

In normal speakers, the dominant speech gradient is resident in the hemisphere centralateral to the preferred hand. Dr. Weisenberg's study on aphasia verified this fact, when he made an analysis of ninety-eight cases of unilateral cerebral lesion. He found that the dominance as shown by handedness is a good criterion of the hemisphere for speech in approximately 95 per cent of the cases. This does not appear to be quite as true with stutterers because from 75 to 90 per cent have been shifted in handedness. We have found that they come from a left-handed stock. In seven hundred clinical stutterers, 83 per cent of them had a history of left-handedness in the family.

Pediatricians can well afford to warn parents not to meddle with the native handedness of children. Left-handedness is a perfectly normal expression in about thirty out of every one hundred children born. It is our present belief that this transfer deranges inherited neural patterns for speech, writing, and reading.

Academy News

The annual meeting of Region IV of the Academy will be held in Seattle on August 9 and 10, 1935. This meeting will take the place of the fall meeting of the North Pacific Pediatric Society.

Dr. J. Lewis Blanton of Fairmont has accepted the chairmanship for West Virginia.

Comments

THE Fifth Annual meeting of the Academy, which will be held at the Waldorf-Astoria Hotel in New York on June 7 and 8, promises to bring together the largest group of pediatricians which has ever assembled in the United States. Although at the time this is written the meeting is two months off, approximately 250 members have already registered for the Round Table Discussions. According to an estimate based on previous meetings, the attendance should reach to between four and five hundred. The final program will reach the members before this comment. The Panel Discussions have been increased as a result of the way they were received and liked at the meeting last year.

One important arrangement that has been made for the first time is the reduced railroad fare on the "certificate plan." Members should buy a one-way ticket to New York and obtain at the same time a "convention certificate." This, when validated at the meeting, entitles the holder to purchase a one-way return ticket at one-third the regular fare. Whether one plans to use the certificate or not, he should obtain it with his one-way fare and have it validated, as convention rates require a certain number of certificates to obtain the reduction.

The commercial exhibit will be larger than in previous years. We urge the members to take the time to go carefully and thoroughly through the exhibit. It helps defray the expenses of the meeting and will be successful only to the extent to which the members show an interest.

Exhibitors

Scientific

	BOOTH
American Child Health Assn. New York City	22
Children's Bureau Washington, D. C.	24
Children's Welfare Federation of New York City, Inc.	23
Department of Health New York City	25

Commercial

	BOOTH
Arch Corrector Corporation	3
Cameron's Surgical Specialty Co.	7
Harold H. Clapp, Inc.	19
R. B. Davis Company	17
The Dry Milk Co., Inc.	13 and 14
Food Concentrates, Inc.	2
Gerber Products Company	A
Health Products Corporation	18
H. J. Heinz Company	1
The Larsen Company	D
Libby, McNeill and Libby	4
J. B. Lippincott Company	6
Mead Johnson & Company	B and C
Medical Case History Bureau	16
Mellin's Food Company	11 and 12
Merck & Co., Inc.	E
The C. V. Mosby Company	15
M. & R. Dietetic Laboratories, Inc.	F
Ralston Purina Company	9
Scientific Sugars Company	8
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